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(54) Title: RANDOM PEPTIDES THAT BIND TO GASTRO-INTESTINAL TRACT (GIT) TRANSPORT RECEPTORS AND RELATED METHODS

(57) Abstract

This invention relates to proteins (e.g., peptides) that are capable of facilitating transport of an active agent through a human or animal gastro-intestinal tissue, and derivatives (e.g., fragments) and analogs thereof, and nucleotide sequences coding for said proteins and derivatives. The proteins of the invention have use in facilitating transport of active agents from the luminal side of the GIT into the systemic blood system, and/or in targeting active agents to the GIT. Thus, for example, by binding (covalently or noncovalently) a protein of the invention to an orally administered drug, the drug can be targeted to specific receptor sites or transport pathways which are known to operate in the human gastro-intestinal tract, thus facilitating its absorption into the systemic system.

20	40	60
MGMSKSHSFFGYPLSIFIV	VNEFCERFSYYGMRAILILY	FTNFISWDDNLSTAIYHTFV
80	100	120
ALCYLTPILGALIADSWLKG	FKTIVLSIVYITGQAVTSV	SSINDLTDHNDGTPDLSLV
140	160	180
HVVLISLIGLALIALGTGGIK	PCVSAFGGQFEEGQEKQRN	RFFSIFYLAINAGSLISTII
200	220	240
TPMLRVQQCGIHSKQACYP	AFGVPAALMAVALIVFVLGS	GMYYKFKPQGNIMGKVAKCI
260	280	300
GFAIKNRFRHRSKAFPKREH	WLDWAKEKYDERLISQIKW	TRVMFLYIPLPMFALFDQQ
320	340	360
GSRWTLQATTMSGKIGALEI	QPDQMVTVNAILIVIMVPIF	DAVLYPLIAKCGFNFTSLKK
380	400	420
MAVGMVLASMAFVVAIVQV	EIDKTLPVFPKGNEVQIKVL	NIGNNTMNISLPGEMVTLGP
440	460	480
MSQTNAFMTFDVNKLTRINI	SSPGSPVTAVTDDFKQGRH	TLLVWAPNHQYVVKDGLNQK
500	520	540
PEKGENGIRFVNTFNELITI	TMSGKVYANISSYNASTYQF	FPSGKIGFTISSTEIPPQCQ
560	580	600
PNFNTFYLEFGSAYTYIVQR	KNDSCPEVKVFEDISANTVN	MAIQIPQYLLTGCGEVVSFV
620	640	660
TGLEFSYSQAPSNMKSVLQA	GWLLTVAVGNIIVLIVAGAG	QFSKQWAEYILFAALLLVVC
680	700	708
VIFAIMARFYTYINPAEIEA	QFDEDEKKNRLEKSNPYFMS	GANSQKQM

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**RANDOM PEPTIDES THAT BIND TO GASTRO-INTESTINAL
TRACT (GIT) TRANSPORT RECEPTORS AND RELATED METHODS**

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This application claims priority to U.S. provisional application Serial No. 60/046,595 filed May 15, 1997, which is incorporated by reference herein in its entirety.

10

1. INTRODUCTION

The present invention relates generally to random peptides capable of specific binding to gastro-intestinal tract (GIT) transport receptors. In particular, this invention relates to peptide sequences and motifs, as well as derivatives thereof, which enhance drug delivery and transport through tissue, such as epithelial cells lining the lumenal side of the gastro-intestinal tract (GIT). Production of peptides, derivatives and antibodies is also provided. The invention further relates to pharmaceutical compositions, formulations and related methods.

2. BACKGROUND OF THE INVENTION

2.1. Peptide Libraries

There have been two different approaches to the construction of random peptide libraries. According to one approach, peptides have been chemically synthesized *in vitro* in several formats. Examples of chemically synthesized libraries can be found in Fodor, S., et al., 1991, Science 251: 767-773; Houghten, R., et al., 1991, Nature 354: 84-86; and Lam, K., et al., 1991, Nature 354: 82-84.

A second approach to the construction of random peptide libraries has been to use the M13 phage, and, in particular, protein pIII of M13. The viral capsid protein of M13, protein III (pIII), is responsible for infection of bacteria. Several investigators have determined from mutational analysis that the 406 amino acid long pIII capsid

protein has two domains. The C-terminus anchors the protein to the viral coat, while portions of the N-terminus of pIII are essential for interaction with the *E. coli* pillin protein (Crissman, J.W. and Smith, G.P., 1984, *Virology* 132: 445-5 455). Although the N-terminus of the pIII protein has shown to be necessary for viral infection, the extreme N-terminus of the mature protein does tolerate alterations. In 1985, George Smith published experiments reporting the use of the pIII protein of bacteriophage M13 as an experimental system 10 for expressing a heterologous protein on the viral coat surface (Smith, G.P., 1985, *Science* 228: 1315-1317). It was later recognized, independently by two groups, that the M13 phage pIII gene display system could be a useful one for mapping antibody epitopes (De la Cruz, V., et al., 1988, 15 *J. Biol. Chem.* 263: 4318-4322; Parmley, S.F. and Smith, G.P., 1988, *Gene* 73: 305-318).

Parmley, S.F. and Smith, G.P., 1989, *Adv. Exp. Med. Biol.* 251: 215-218 suggested that short, synthetic DNA segments cloned into the pIII gene might represent a library 20 of epitopes. These authors reasoned that since linear epitopes were often ~6 amino acids in length, it should be possible to use a random recombinant DNA library to express all possible hexapeptides to isolate epitopes that bind to antibodies. Scott, J.K. and Smith, G.P., 1990, *Science* 249: 25 386-390 describe construction and expression of an "epitope library" of hexapeptides on the surface of M13. Cwirla, S.E., et al., 1990, *Proc. Natl. Acad. Sci. USA* 87: 6378-6382 also described a somewhat similar library of hexapeptides expressed as gene pIII fusions of M13 fd phage. PCT 30 Application WO 91/19818 published December 26, 1991 by Dower and Cwirla describes a similar library of pentameric to octameric random amino acid sequences. Devlin et al., 1990, *Science*, 249: 404-406, describes a peptide library of about 15 residues generated using an (NNS) coding scheme for 35 oligonucleotide synthesis in which S is G or C. Christian and colleagues have described a phage display library,

expressing decapeptides (Christian, R.B., et al., 1992, J. Mol. Biol. 227: 711-718).

Other investigators have used other viral capsid proteins for expression of non-viral DNA on the surface of 5 phage particles. For example, the major capsid protein pVIII was so used by Cesareni, G., 1992, FEBS Lett. 307: 66-70. Other bacteriophage than M13 have been used to construct peptide libraries. Four and six amino acid sequences corresponding to different segments of the Plasmodium 10 falciparum major surface antigen have been cloned and expressed in the filamentous bacteriophage fd (Greenwood, J., et al., 1991, J. Mol. Biol. 220: 821-827).

Kay et al., 1993, Gene 128: 59-65 (Kay) discloses a method of constructing peptide libraries that encode peptides 15 of totally random sequence that are longer than those of any prior conventional libraries. The libraries disclosed in Kay encode totally synthetic random peptides of greater than about 20 amino acids in length. Such libraries can be advantageously screened to identify peptides, polypeptides 20 and/or other proteins having binding specificity for a variety of ligands. (See also U.S. Patent No. 5,498,538 dated March 12, 1996; and PCT Publication No. WO 94/18318 dated August 18, 1994.)

A comprehensive review of various types of peptide 25 libraries can be found in Gallop et al., 1994, J. Med. Chem. 37:1233-1251.

Screening of peptide libraries has often been done using an antibody as ligand (Parmley and Smith, 1989, Adv. Exp. Med. Biol. 251:215-218; Scott and Smith, 1990, 30 Science 249:386-390). In many cases, the aim of the screening is to identify peptides from the library that mimic the epitopes to which the antibodies are directed. Thus, given an available antibody, peptide libraries are excellent sources for identifying epitopes or epitope-like molecules of 35 that antibody (Yayon et al., 1993, Proc. Natl. Acad. Sci. USA 90:10643-10647).

McCafferty et al., 1990, Nature 348:552-554 used PCR to amplify immunoglobulin variable (V) region genes and cloned those genes into phage expression vectors. The authors suggested that phage libraries of V, diversity (D),
5 and joining (J) regions could be screened with antigen. The phage that bound to antigen could then be mutated in the antigen-binding loops of the antibody genes and rescreened. The process could be repeated several times, ultimately giving rise to phage which bind the antigen strongly.

10 Marks et al., 1991, J. Mol. Biol. 222:581-597 also used PCR to amplify immunoglobulin variable (V) region genes and cloned those genes into phage expression vectors.

Kang et al., 1991, Proc. Natl. Acad. Sci. USA 88:4363-4366 created a phagemid vector that could be used to
15 express the V and constant (C) regions of the heavy and light chains of an antibody specific for an antigen. The heavy and light chain V-C regions were engineered to combine in the periplasm to produce an antibody-like molecule with a functional antigen binding site. Infection of cells
20 harboring this phagemid with helper phage resulted in the incorporation of the antibody-like molecule on the surface of phage that carried the phagemid DNA. This allowed for identification and enrichment of these phage by screening with the antigen. It was suggested that the enriched phage
25 could be subject to mutation and further rounds of screening, leading to the isolation of antibody-like molecules that were capable of even stronger binding to the antigen.

Hoogenboom et al., 1991, Nucleic Acids Res. 19:4133-4137 suggested that naive antibody genes might be
30 cloned into phage display libraries. This would be followed by random mutation of the cloned antibody genes to generate high affinity variants.

Bass et al., 1990, Proteins: Struct. Func. Genet. 8:309-314 fused human growth hormone (hGH) to the carboxy
35 terminus of the gene III protein of phage fd. This fusion protein was built into a phagemid vector. When cells carrying the phagemid were infected with a helper phage,

about 10% of the phage particles produced displayed the fusion protein on their surfaces. These phage particles were enriched by screening with hGH receptor-coated beads. It was suggested that this system could be used to develop mutants
5 of hGH with altered receptor binding characteristics.

Lowman et al., 1991, Biochemistry 30:10832-10838 used an improved version of the system of Bass et al. described above to select for mutant hGH proteins with exceptionally high affinity for the hGH receptor. The
10 authors randomly mutagenized the hGH-pIII fusion proteins at sites near the vicinity of 12 amino acids of hGH that had previously been identified as being important in receptor binding.

Balass et al., 1993, Proc. Natl. Acad. Sci. USA
15 90:10638-10642 used a phage display library to isolate linear peptides that mimicked a conformationally dependent epitope of the nicotinic acetylcholine receptor. This was done by screening the library with a monoclonal antibody specific for the conformationally dependent epitope. The monoclonal
20 antibody used was thought to be specific to the acetylcholine receptor's binding site for its natural ligand, acetylcholine.

2.2. Drug Delivery Systems

25 The common routes of therapeutic drug administration are oral ingestion or parenteral (intravenous, subcutaneous and intramuscular) routes of administration. Intravenous drug administration suffers from numerous limitations, including (i) the risk of adverse effects
30 resulting from rapid accumulation of high concentrations of drug, (ii) repeated injections which can cause patient discomfort; and (iii) the risk of infection at the site of repeated injections. Subcutaneous injection is not generally suitable for delivering large volumes or for irritating
35 substances. Whereas oral administration is generally more convenient, it is limited where the therapeutic agent is not efficiently absorbed by the gastrointestinal tract. To date,

the development of oral formulations for the effective delivery of peptides, proteins and macromolecules has been an elusive target. Poor membrane permeability, enzymatic instability, large molecular size, and hydrophilic properties are four factors that have remained major hurdles for peptide and protein formulations (reviewed by Fix, J.A., 1996, J. Pharmac. Sci. 85:1282-1285). In order to develop an efficacious oral formulation, the peptide must be protected from the enzymatic environment of the gastrointestinal tract (GIT), presented to the absorptive epithelial barrier in a sufficient concentration to effect transcellular flux (Fix, J.A., 1996, J. Pharmac. Sci. 85:1282-1285), and if possible "smuggled" across the epithelial barrier in an apical to basolateral direction.

Site specific drug delivery or drug targeting can be achieved at different levels, including (i) primary targeting to a specific organ, (ii) secondary targeting to a specific cell type within that organ and (iii) tertiary targeting where the drug is delivered to specific intracellular structures (e.g., the nucleus for genes) (reviewed in Davis and Jllum, 1994, In: Targeting of Drugs 4, (Eds), Gregoriadis, McCormack and Poste, 183-194). At present there is a considerable amount of ongoing research work in the Drug Delivery Systems (DDS) area, and much of it addresses (i) targeting delivery and (ii) the development of non-invasive ways of getting macromolecules, peptides, proteins, products of the biotechnology industry, etc. into the body (Evers, P., 1995, Developments in Drug Delivery: Technology and Markets, Financial Times Management Report). It is generally accepted that targeted drug delivery is crucial to the improved treatment of certain diseases, especially cancer, and not surprisingly many of the approaches to targeted drug delivery are focused in the cancer area. Many anticancer drugs are toxic to the body as well as to malignant cells. If a drug, or a delivery system, can be modified so that it "homes in" on the tumor, then by maximizing the drug concentration at the disease site, the

anti-cancer effect can be exploited to the full, while toxicity is greatly reduced. Tumors contain antigens which provoke the body to respond by producing antibodies designed to attach to the antigens and destroy them. Monoclonal
5 antibodies are being used as both delivery vehicles targeted to tumor cells (reviewed by Pietersz, G.A., 1990, Bioconjugate Chem. 1:89-95) and as imaging agents to carry molecules of drug or imaging agent to the tumor surface.

10 2.3. Transport Pathways

The epithelial cells lining the luminal side of the GIT are a major barrier to drug delivery following oral administration. However, there are four recognized transport pathways which can be exploited to facilitate drug delivery
15 and transport: the transcellular, paracellular, carrier-mediated, and transcytotic pathways. The ability of a conventional drug, peptide, protein, macromolecule or nano- or microparticulate system to "interact" with one of these transport pathways may result in increased delivery of that
20 drug or particle from the GIT to the underlying circulation.

In the case of the receptor-mediated, carrier-mediated or transcytotic transport pathways, some of the uptake signals have been identified. These signals include, *inter alia*, folic acid, which interacts with the folate
25 receptor, and cobalamin, which interacts with Intrinsic Factor. In addition, leucine- and tyrosine-based peptide sorting motifs or internalization sequences exist, such as YSKV, FPHL, YRGV, YQTI, TEQF, TEVM, TSAF, and YTRF (SEQ ID NOS:203, 204, 205, 206, 207, 208, 209, and 210,
30 respectively), which facilitate uptake or targeting of proteins using specific membrane receptors or binding sites to identify peptides that bind specifically to the receptor or binding site.

Non-receptor based assays to discover particular
35 ligands have also been used. For instance, a strategy for identifying peptides that alter cellular function by scanning whole cells with phage display libraries is disclosed in Fong

et al., Drug Development Research 33:64-70 (1994). However, because whole cells, rather than intact tissue or polarized cell cultures, are used for screening phage display libraries, this procedure does not provide information
5 regarding sequences whose primary function includes affecting transport across polarized cell layers.

Additionally, Stevenson et al., Pharmaceutical Res. 12(9), S94 (1995) discloses the use of Caco-2 monolayers to screen a synthetic tripeptide combinatorial library for
10 information relating to the permeability of di- and tri-peptides.

A method of identifying a peptide which permits or facilitates the transport of an active agent through human or animal tissues has been developed (see U.S. patent
15 application Serial No. 08/746,411 filed November 8, 1996, which is incorporated by reference herein in its entirety). Phage from a random phage library is plated onto or brought into contact with a first side, preferably the apical side, of a tissue sample, either *in vitro*, *in vivo* or *in situ*, or
20 polarized tissue cell culture. The phage which is transported to a second side of the tissue opposite the first side, preferably the basolateral side, is harvested to select transported phages. The transported phages are amplified in a host and this cycle is repeated (using the transported
25 phage from the most recent cycle) to obtain a selected phage library containing phage which can be transported from the first side to the second side.

Discussion or citation of a reference hereinabove shall not be construed as meaning that such reference is
30 prior art to the present invention.

3. SUMMARY OF THE INVENTION

The present invention relates generally to random peptides and peptide motifs capable of specific binding to
35 GIT transport receptors. Such proteins can be identified using any random peptide library, e.g., a chemically synthesized peptide library or a biologically expressed

peptide library. If a biological peptide expression library is used, the nucleic acid which encodes the peptide which binds to the ligand of choice can be recovered, and then sequenced to determine its nucleotide sequence and hence
5 deduce the amino acid sequence that mediates binding.

Alternatively, the amino acid sequence of an appropriate binding domain can be determined by direct determination of the amino acid sequence of a peptide selected from a peptide library containing chemically synthesized peptides. In a
10 less preferred aspect, direct amino acid sequencing of a binding peptide selected from a biological peptide expression library can also be performed.

In particular, this invention relates to proteins (e.g., peptides) that are capable of facilitating transport
15 of an active agent through a human or animal gastrointestinal tissue, and derivatives (e.g., fragments) and analogs thereof, and nucleotide sequences coding for said proteins and derivatives.

Preferably, the tissue through which transport is
20 facilitated is of the duodenum, jejunum, ileum, ascending colon, transverse colon, descending colon, or pelvic colon. The tissue is most preferably epithelial cells lining the luminal side of the GIT.

The proteins of the invention have use in
25 facilitating transport of active agents from the luminal side of the GIT into the systemic blood system, and/or in targeting active agents to the GIT. Thus, for example, by binding (covalently or noncovalently) a protein of the invention to an orally administered drug, the drug can be
30 targeted to specific receptor sites or transport pathways which are known to operate in the human gastrointestinal tract, thus facilitating its absorption into the systemic system.

The invention also relates to derivatives and
35 analogs of the invention which are functionally active, i.e., they are capable of displaying one or more known functional activities associated with a full-length peptide. Such

functional activities include but are not limited to antigenicity (ability to bind or to compete with GIT transport receptor-binding peptides for binding to an anti-GIT transport receptor antibody) and ability to bind or
5 compete with full-length peptide for binding to a GIT transport receptor.

The invention further relates to fragments of (and derivatives and analogs thereof) GIT transport receptor-binding peptides which comprise one or more motifs of a GIT
10 transport receptor-binding peptide.

Antibodies to GIT transport receptor-binding peptides and GIT transport receptor-binding peptide derivatives and analogs are additionally provided.

Methods of production of the GIT transport
15 receptor-binding peptides, derivatives, fragments and analogs, e.g., by recombinant means, are also provided.

The present invention also relates to therapeutic methods, pharmaceutical compositions and formulations based on GIT transport receptor-binding peptides. Formulations of
20 the invention include but are not limited to GIT transport receptor-binding peptides or motifs and derivatives (including fragments) thereof; antibodies thereto; and nucleic acids encoding the GIT transport receptor-binding peptides or derivatives associated with an active agent.
25 Preferably, the active agent is a drug or drug-containing nano- or microparticle.

The GIT transport-receptor binding proteins of the invention can also be used to determine levels of the GIT transport receptors in a sample by binding thereto.

30 The GIT transport-receptor binding proteins can also be used to identify molecules that bind thereto, by contacting candidate test molecules under conditions conducive to binding, and detecting any binding that occurs.

35 4. DESCRIPTION OF THE FIGURES

Figure 1. Figure 1 shows the human PEPT1 predicted amino acid sequence determined from the sequence of the cDNA clone

coding for human PEPT1 (SEQ ID NO:176) (Liang R. et al. J. Biol. Chem. 270(12):6456-6463 (1995)), including the extracellular domain from amino acid 391 to 573 (Fei et al., Nature 368:563 (1994)).

- 5 **Figures 2A-2C.** Figures 2A-2C show the DNA sequence of the cDNA coding for the human intestinal peptide-associated transporter HPT1 and the corresponding putative amino acid sequence (bases 1 to 3345; Medline:94204643) (SEQ ID NOS: 177 and 178, respectively).
- 10 **Figures 3A-3B.** Figures 3A-3B show the putative Human Sucrase-isomaltase complex(hSI) amino acid sequence determined from the sequence of the cDNA clone coding for human sucrase-isomaltase complex (SEQ ID NO:179) (Chantret I., et al., Biochem. J. 285(Pt 3):915-923 (1992)).
- 15 **Figures 4A-4B.** Figures 4A-4B show the D2H nucleotide and deduced amino acid sequence for the human D2H transporter (SEQ ID NOS:180 and 181, respectively) (Wells, R.G. et al., J. Clin. Invest. 90:1959-1963 (1993)).
- Figures 5A-5C.** Figure 5A is a schematic summary of the
- 20 cloning of the DNA insert present in gene III of the phages selected from the phage display libraries into the expression vector pGex-4T-2. The gene insert in gene III of the phages was amplified by PCR using DNA primers which flank the gene insert and which contained recognition sequences for specific
- 25 restriction endonucleases at their extreme 5' sides. Alternatively, specific primers which amplify specific regions of the DNA inserts in gene III of the phages, and which contained recognition sequences for specific
- 30 restriction endonucleases at their extreme 5' sides, were used in PCR amplification experiments. Following amplification of the gene inserts, the amplified PCR fragments were digested with the restriction endonucleases Xho1 and Not1. Similarly the plasmid pGex-4T-2, which codes for the reporter protein glutathione S-transferase (GST), was
- 35 digested with the restriction endonucleases Sal1 and Not1. The digested PCR fragments were ligated into the digested plasmid pGex-4T-2 using T4 DNA Ligase and the ligated

products were transformed into competent *Escherichia coli*, with selection of transformants on agar plates containing selection antibiotic. The selected clones were cultured, the plasmids were recovered and the in-frame sequence of the DNA insert in the plasmids was confirmed by DNA sequencing. The correct clones were subsequently used for expression of the GST-fusion proteins (SEQ ID NO:182); Figure 5B shows the series of full-length P31 (designated P31) (SEQ ID NO:43) and truncated peptides derived from P31 (clones # 101, 102, 103 and 119), (SEQ ID NOS:183, 184, 185, and 186, respectively) full-length PAX2 (designated PAX2) (SEQ ID NO:55) and truncated peptides derived from PAX2 (clones # 104, 105, 106) (SEQ ID NOS:170, 187, and 188, respectively) and full-length DCX8 (DCX8) (SEQ ID NO:23) and series of truncated peptides derived from DCX8 (clones # 107, 108, 109) (SEQ ID NOS:189, 190, and 191, respectively) that were expressed as fusion proteins to GST. The construction of these GST-fusion proteins is shown in Figure 5A. Figure 5C shows the series of full-length P31 (designated P31) (SEQ ID NO:43) and truncated peptides derived from P31 (clones # 103, 110, 119, 111, and 112) (SEQ ID NOS:185, 192, 193, 194, and 195, respectively), full-length PAX2 (designated PAX2) (SEQ ID NO:55) and truncated peptides derived from PAX2 (clones # 106, 113, 114, 115) (SEQ ID NOS:188, 196, 197, and 198, respectively) and full-length SNI10 (designated SNI10) (SEQ ID NO:4) and series of truncated peptides derived from SNI10 (clones # 116, 117, 118) (SEQ ID NOS:199, 200, and 201, respectively) that were expressed as fusion proteins to GST. The construction of these GST-fusion proteins is shown in Figure 5A. (Underlining and bold in Figs. 5A-5C are for orientation of the sequences.)

Figures 6A-6B. Figures 6A-6B show the binding of GST and GST-fusion proteins to recombinant hSI and to fixed C2BBel fixed cells as detected by ELISA assays. Figure 6A shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from SNI10 (designated GST-SNI10) and SNI34 (designated GST-SNI34) to

recombinant hSI. Figure 6B shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from SNI10 (designated GST-SNI10) and SNI34 (designated GST-SNI34) to fixed C2BBel cells.

5 **Figures 7A-7M.** Figures 7A-7M show the binding of GST peptide and truncated fusion proteins to fixed Caco-2 cells, fixed C2BBel cells, and fixed A431 cells or to recombinant GIT transport receptors D2H, HPT1, hPEPT1 or to BSA using increasing concentrations (expressed as $\mu\text{g/ml}$ on the X-axis)
10 of the control GST protein and the GST-fusion proteins, as detected by ELISA assays. Figure 7A shows the binding of the control protein GST, which does not contain a fusion peptide, and the series of GST-fusion proteins from P31 including the fusion to full-length P31 peptide (designated P31) (SEQ ID
15 NO:43) and clone # 101 (designated P31,101), clone # 102 (designated P31, 102) and clone # 103 (designated P31,103). Figure 7B shows the binding of the control protein GST, which does not contain a fusion peptide, and the series of GST-fusion proteins from PAX2 including the fusion to full-length
20 PAX2 peptide (designated PAX2) and clone # 104 (designated PAX2,104), clone # 105 (designated PAX2, 105) and clone # 106 (designated PAX2,106) (SEQ ID NOS:55, 170, 187, and 188, respectively). Figure 7C shows the binding of the control
25 series of GST-fusion proteins from DCX8 including the fusion to full-length DCX8 peptide (designated DCX8) and clone # 107 (designated DCX8,107), clone # 108 (designated DCX8, 108) and clone # 109 (designated DCX8,109) (SEQ ID NOS:23, 189, 190, and 191, respectively). Figure 7D shows the binding of the
30 control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from DCX8 (designated GST-DCX8) and DCX11 (designated GST-DCX11) to recombinant D2H. Figure 7E shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins
35 from DCX8 (designated GST-DCX8) and DCX11 (designated GST-DCX11) to fixed C2BBel cells. Figure 7F shows the binding of the control protein GST, which does not contain a fusion

peptide, and the GST-fusion proteins from P31 (designated GST-P31) and 5PAX5 (designated GST-5PAX5) to recombinant hPEPT1. Figure 7G shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-5 fusion proteins from P31 (designated GST-P31) and 5PAX5 (designated GST-5PAX5) to fixed C2BBel cells. Figure 7H shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from HAX42 (designated GST-HAX42) and PAX2 (designated GST-PAX2) to recombinant HPT1. Figure 7I shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from HAX42 (designated GST-HAX42) and PAX2 (designated GST-PAX2) to fixed C2BBel cells. Figure 7J shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from P31 (designated GST-P31) and truncated derivatives clone # 101 (designated GST-P31-101), clone # 102 (designated GST-P31-102), clone # 103 (designated GST-P31-103) to either recombinant hPEPT1 or to BSA. Figure 7K shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from P31 (designated GST-P31) and truncated derivatives clone # 101 (designated GST-P31-101), clone # 102 (designated GST-P31-102), clone # 103 (designated GST-P31-103) to either fixed C2BBel cells or to fixed A431 cells. Figure 7L shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from PAX2 (designated GST-PAX2) and truncated derivatives clone # 104 (designated GST-PAX2-104), clone # 105 (designated GST-PAX2-105), clone # 106 (designated GST-PAX2-106) to either recombinant hPEPT1 or to BSA. Figure 7M shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from PAX2 (designated GST-PAX2) and truncated derivatives clone # 106 (designated GST-PAX2-106) to either fixed Caco-2 cells or to fixed A431 cells.

Figures 8A-8D. Figure 8 shows the transport of GST or GST-peptide fusion derivatives across polarized Caco-2 cells in

an apical to basolateral direction as a function of time (1-4 hours) as detected by ELISA assays. Figure 8A shows the transport of either GST, the GST fusion to full-length P31 peptide (designated P31) (SEQ ID NO:43) and the GST clone derivative clone # 103 (designated P31.103) across polarized
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Caco-2 cells in an apical to basolateral as a function of time (in hours) following initial administration of the proteins to the apical medium of polarized Caco-2 cells. The line designated No Protein corresponds to control assays in
10
which buffer control was applied to the apical medium of polarized Caco-2 cells followed by sampling of the basolateral medium as a function of time (hours) and assay for GST by the ELISA assay. Figure 8B shows the transport of either GST, the GST fusion to full-length PAX2 peptide
15
(designated PAX2) and the GST clone derivative clone # 106 (designated PAX2.106) across polarized Caco-2 cells in an apical to basolateral as a function of time (in hours) following initial administration of the proteins to the apical medium of polarized Caco-2 cells. The line designated
20
No Protein corresponds to control assays in which buffer control was applied to the apical medium of polarized Caco-2 cells followed by sampling of the basolateral medium as a function of time (hours) and assay for GST by the ELISA
assay. Figure 8C shows the transport of either GST, the GST
25
fusion to full-length DCX8 peptide (designated DCX8), and the GST clone derivatives clone # 107 (designated DCX8.107) and clone # 109 (designated DCX8.109) across polarized Caco-2 cells in an apical to basolateral as a function of time (in hours) following initial administration of the proteins to
30
the apical medium of polarized Caco-2 cells. The line designated No Protein corresponds to control assays in which buffer control was applied to the apical medium of polarized Caco-2 cells followed by sampling of the basolateral medium as a function of time (hours) and assay for GST by the ELISA
35
assay. Figure 8D shows the amount of the GST and GST-fusion proteins (GST fusions to P31, P31-103, PAX2, PAX2.106, DCX8, DCX8-107, DCX8-109), used in the experiments shown in panels

A-C above, in the apical medium of the polarized Caco-2 cells as detected by ELISA assay.

Figures 9A-9B. Figures 9A-9B show the inhibition of GST-P31 binding to C2BBel fixed cells with varying concentration of 5 competitors while holding the concentration of GST-P31 constant at 0.015 μ M; the peptide competitors are ZElan024 which is the dansylated peptide version of P31 (SEQ ID NO:43) and ZElan044, ZElan049 and ZElan050 which are truncated, dansylated pieces of P31 (SEQ ID NO:43). Data is presented 10 as O.D. versus peptide concentration (Figure 9A) and as percent inhibition of GST-P31 binding versus peptide concentration (Figure 9B).

Figures 10A-10C. Figures 10A-10C present a compilation of the results of competition ELISA studies of GST-P31, GST- 15 PAX2, GST-SNi10 and GST-HAX42 versus listed dansylated peptides on fixed C2BBel cells ("Z" denotes ϵ -amino dansyl lysine). The pI of the dansylated peptides is also included. Estimated IC₅₀ values are in μ M and where present, IC₅₀ ranges refer to results from multiple assays. If the IC₅₀ value 20 could not be determined, a ">" or "<" symbol is used. The GST/C2BBel column shows GST protein binding to fixed C2BBel cells.

Figures 11A-11B. Figure 11A shows the transport of GST or GST-peptide fusion derivatives across polarized Caco-2 cells 25 in an apical to basolateral direction at 0, 0.5, 2 and 4 hours as detected by ELISA assays and described elsewhere in the text in full detail. The proteins used in the assay included GST, GST-P31 fusion, GST-5PAX5 fusion, GST-DCX8 fusion, GST-DCX11 fusion, GST-PAX2 fusion, GST-HAX42 fusion, 30 GST-SNi34 fusion and GST-SNi10 fusion. The column designated No protein refers to control experiments in which buffer was applied to the apical medium of the cells and ELISA assay was performed on the corresponding basolateral medium of these cells at 0, 0.5, 2 and 4 hours post buffer addition. Figure 35 11B shows the internalization of GST or GST-peptide fusion derivatives within polarized Caco-2 cells following administration of the GST or GST-fusion protein derivatives

to the apical medium of polarized Caco-2 cells and subsequent recovery of the cells from the transwells and detection of the GST or GST fusions within the recovered cell lysates as detected by ELISA assays and as described elsewhere in the text in full detail. The proteins used in the assay included GST, GST-P31 fusion, GST-5PAX5 fusion, GST-DCX8 fusion, GST-DCX11 fusion, GST-PAX2 fusion, GST-HAX42 fusion, GST-SNi34 fusion and GST-SNi10 fusion. The column designated No protein refers to control experiments in which buffer was applied to the apical medium of the cells and ELISA assay was performed on the corresponding cell lysates of these cells at the end of the experiment.

Figure 12. Figure 12 shows the binding of GST and GST-fusion proteins to fixed Caco-2 cells, and the corresponding proteins following digestion with the protease Thrombin which cleaves at a recognition site between the GST portion and the fused peptide portion of the GST-fusion protein. The symbol "-" refers to proteins which were not digested with thrombin and the symbol "+" refers to proteins which were digested with thrombin prior to use in the binding assay. The binding of the proteins to the fixed Caco-2 cells was detected by ELISA assays.

Figures 13A-13B. Figures 13A-13B show binding of peptide-coated nanoparticles to fixed Caco-2 cells.

Figures 14A-14B. Figures 14A-14B show the binding of (A) dansylated peptide SNi10 to the purified hSI receptor and BSA and (B) dansylated peptides and peptide-loaded insulin-containing PLGA particles to fixed C2BBel cells. Figure 14B depicts binding of dansylated peptides corresponding to P31 (SEQ ID NO:43), PAX2, HAX42, and SNi10 to fixed C2BBel cells, as well as the insulin-containing PLGA particles adsorbed with each of these peptides. Data is presented with background subtracted.

Figures 15A-15B. Figure 15 shows the binding of peptide-coated particles to A) S100 and B) P100 fractions harvested from Caco-2 cells. The dilution series 1:2 - 1:64 represents particle concentrations in the range 0.0325-0.5 μ g/well.

Data is presented with background subtracted. The particles are identified as follows: 939, no peptide; 1635, scrambled PAX2; 1726, P31 D-Arg 16-mer (ZElan053); 1756, HAX42; 1757, PAX2; 1758, HAX42/PAX2.

5 **Figures 16A-16B.** Figure 16 shows the binding of dansylated peptides to P100 fractions harvested from Caco-2 cells. Peptides were assayed in the range 0.0032-2.5 μ g/well. Data is presented with background subtracted. A) HAX42, P31 D-form (ZElan 053) and scrambled PAX2; B) PAX2, HAX42 and
10 scrambled PAX2.

Figures 17A-17B. Figures 17A and 17B show (A) the systemic blood glucose and (B) insulin levels following intestinal administration of control (PBS); insulin solution; insulin particles; all 8 peptide mix particles and study group
15 peptide-particles according to this invention (100iu insulin loading).

Figures 18A-18B. Figures 18A and 18B show the (A) systemic blood glucose and (B) insulin levels following intestinal administration of control (PBS); insulin solution; insulin
20 particles and study group peptide-particles according to this invention (300iu insulin loading).

Figure 19. Figure 19 shows the enhanced plasma levels of leuprolide upon administration of P31 (SEQ ID NO:43) and PAX2 coated nanoparticles loaded with leuprolide relative to
25 subcutaneous injection. Group 1 was administered leuprolide acetate (12.5 μ g) subcutaneously. Group 2 was administered intraduodenally uncoated leuprolide acetate particles (600 μ g, 1.5 ml). Group 3 was intraduodenally administered leuprolide acetate particles coated with PAX2 (600 μ g; 1.5
30 ml). Group 4 was administered intraduodenally leuprolide acetate particles coated with P31 (SEQ ID NO:43) (600 μ g, 1.5 ml).

Figure 20. Figure 20 lists P31 (SEQ ID NO:43) known protein homologies.

35 **Figures 21A-21C.** Figures 21A-21C list DCX8 known protein homologies.

Figure 22. Figure 22 lists DAB10 known protein homologies.

Figure 23. Figure 23 shows the DNA sequence (SEQ ID NO:211) and the corresponding amino acid sequence (SEQ ID NO:212) for glutathione S-transferase (Smith and Johnson, 1988, Gene 7:31-40).

5

5. DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to proteins (e.g., peptides) that bind to GIT transport receptors and nucleic acids that encode such proteins. The invention further
10 relates to fragments and other derivatives of such proteins. Nucleic acids encoding such fragments or derivatives are also within the scope of the invention. The invention further relates to fragments (and derivatives and analogs thereof) of GIT transport receptor-binding peptides which comprise one or
15 more domains of the GIT transport receptor-binding peptides.

The invention also relates to derivatives of GIT transport receptor-binding proteins and analogs of the invention which are functionally active, i.e., they are capable of displaying one or more known functional activities
20 associated with a full-length GIT transport receptor-binding peptide. Such functional activities include but are not limited to ability to bind to a GIT transport receptor, antigenicity [ability to bind (or compete with peptides for binding) to an anti-GIT transport receptor-binding peptide
25 antibody], immunogenicity (ability to generate antibody which binds to GIT transport receptor-binding peptide), etc.

Production of the foregoing proteins and derivatives, by, e.g., recombinant methods, is also provided.

Antibodies to GIT transport receptor-binding
30 proteins, derivatives and analogs, are additionally provided.

The present invention also relates to therapeutic and diagnostic methods and compositions based on GIT transport receptor-binding proteins and nucleic acids.

The invention is illustrated by way of examples
35 *infra*.

For clarity of disclosure, and not by way of limitation, the detailed description of the invention is divided into the subsections which follow.

5 **5.1. GIT Transport Receptor-Binding Peptides,
 Derivatives and Analogs**

 The invention relates to peptides that bind GIT transport receptors and derivatives (including but not limited to fragments) and analogs thereof. In specific
10 embodiments, of the present invention, such peptides that bind to GIT transport receptor include but are not limited to those containing as primary amino acid sequences, all or part of the amino acid sequences substantially as depicted in Table 7 (SEQ ID NOS:1-55). Nucleic acids encoding such
15 peptides, derivatives and peptide analogs are also provided. In one embodiment, the GIT transport receptor-binding peptides are encoded by the nucleic acids having the nucleotide sequences set forth in Table 8 *infra* (SEQ ID NOS:56-109). Proteins whose amino acid sequence comprise, or
20 alternatively, consist of SEQ ID NOS:1-55 or a portion thereof that mediates binding to a GIT transport receptor are provided.

 The production and use of derivatives and analogs related to GIT transport receptor-binding peptides are within
25 the scope of the present invention. In a specific embodiment, the derivative or analog is functionally active, *i.e.*, capable of exhibiting one or more functional activities associated with a full-length GIT transport receptor-binding peptide. For example, such derivatives or analogs which have
30 the desired immunogenicity or antigenicity can be used, in immunoassays, for immunization, etc. A specific embodiment relates to a GIT transport receptor-binding peptide fragment that can be bound by an anti-GIT transport receptor-binding peptide antibody. In a preferred aspect, the derivatives or
35 analogs have the ability to bind to a GIT transport receptor. Derivatives or analogs of GIT transport receptor-binding peptides can be tested for the desired activity by procedures

known in the art, including binding to a GIT transport receptor domain or to Caco-2 cells, *in vitro*, or to intestinal tissue, *in vivo*. (See the Examples *infra*.)

In particular, derivatives can be made by altering
5 GIT transport receptor-binding peptide sequences by substitutions, additions or deletions that provide for functionally equivalent molecules. Due to the degeneracy of nucleotide coding sequences, other nucleotide sequences which encode substantially the same amino acid sequence may be used
10 in the practice of the present invention. These include but are not limited to nucleotide sequences which are altered by the substitution of different codons that encode a functionally equivalent amino acid residue within the sequence, thus producing a silent change. Likewise, the GIT
15 transport receptor-binding peptide derivatives of the invention include, but are not limited to, those containing, as a primary amino acid sequence, all or part of the amino acid sequence of a GIT transport receptor-binding peptide including altered sequences in which functionally equivalent
20 amino acid residues are substituted for residues within the sequence resulting in a silent change. For example, one or more amino acid residues within the sequence can be substituted by another amino acid of a similar polarity which acts as a functional equivalent, resulting in a silent
25 alteration. Substitutes for an amino acid within the sequence may be selected from other members of the class to which the amino acid belongs. For example, the nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and
30 methionine. The polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine. The positively charged (basic) amino acids include arginine, lysine and histidine. The negatively charged (acidic) amino acids include aspartic acid and
35 glutamic acid.

In a specific embodiment of the invention, proteins consisting of or, alternatively, comprising all or a fragment

of a GIT transport receptor-binding peptide consisting of at least 5, 10, 15, 20, 25, 30 or 35 (contiguous) amino acids of the full-length GIT transport receptor-binding peptide are provided. In a specific embodiment, such proteins are not
5 more than 20, 30, 40, 50, or 75 amino acids in length.

Derivatives or analogs of GIT transport receptor-binding peptides include but are not limited to those molecules comprising regions that are substantially homologous to GIT transport receptor-binding peptides or fragments thereof
10 (e.g., at least 50%, 60%, 70%, 80% or 90% identity) (e.g., over an identical size sequence or when compared to an aligned sequence in which the alignment is done by a computer homology program known in the art) or whose encoding nucleic acid is capable of hybridizing to a coding GIT transport
15 receptor-binding peptide sequence, under stringent, moderately stringent, or nonstringent conditions.

In a specific embodiment, the GIT transport receptor-binding derivatives of the invention are not known proteins with homology to the GIT transport receptor-binding
20 peptides of the invention or portions thereof.

The GIT transport receptor-binding peptide derivatives and analogs of the invention can be produced by various methods known in the art. The manipulations which result in their production can occur at the gene or protein
25 level. For example, the cloned GIT transport receptor-binding peptide gene sequence can be modified by any of numerous strategies known in the art (Maniatis, T., 1990, Molecular Cloning, A Laboratory Manual, 2d ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York). The
30 sequence can be cleaved at appropriate sites with restriction endonuclease(s), followed by further enzymatic modification if desired, isolated, and ligated *in vitro*. In the production of the gene encoding a derivative or analog of GIT transport receptor-binding peptides, care should be taken to
35 ensure that the modified gene remains within the same translational reading frame uninterrupted by translational

stop signals, in the gene region where the desired GIT transport receptor-binding peptides activity is encoded.

Additionally, nucleic acid sequences encoding the GIT transport receptor-binding peptides can be mutated *in vitro* or *in vivo*, to create and/or destroy translation, initiation, and/or termination sequences, or to create variations in coding regions and/or form new restriction endonuclease sites or destroy preexisting ones, to facilitate further *in vitro* modification. Any technique for mutagenesis known in the art can be used, including but not limited to, chemical mutagenesis, *in vitro* site-directed mutagenesis (Hutchinson, C., et al., 1978, J. Biol. Chem 253:6551), use of TAB® linkers (Pharmacia), use of PCR primers containing mutation(s) for use in amplification, etc.

Manipulations of GIT transport receptor-binding peptide sequences may also be made at the protein level. Included within the scope of the invention are GIT transport receptor-binding peptide fragments or other derivatives or analogs which are differentially modified during or after translation or chemical synthesis, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH₄; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc. In a specific embodiment, the amino- and/or carboxy-termini are modified.

In addition, GIT transport receptor-binding peptides and analogs and derivatives thereof can be chemically synthesized. For example, a peptide corresponding to all or a portion of a GIT transport receptor-binding peptide which comprises the desired domain or which mediates the desired activity *in vitro*, can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical

amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the GIT transport receptor-binding peptide sequence. Non-classical amino acids include but are not limited to the D-isomers of the common
5 amino acids, α -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, γ -Abu, ϵ -Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, cysteic acid, t-butylglycine, t-butylalanine,
10 phenylglycine, cyclohexylalanine, β -alanine, fluoro-amino acids, designer amino acids such as β -methyl amino acids, C α -methyl amino acids, N α -methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

15 In a specific embodiment, the GIT transport receptor-binding peptide derivative is a chimeric, or fusion, peptide comprising a GIT transport receptor-binding peptide or fragment thereof (preferably consisting of at least a domain or motif of the GIT transport receptor-binding
20 peptide, or at least 6, 10, 15, 20, 25, 30 or all amino acids of the GIT transport receptor-binding peptides or a binding portion thereof) joined at its amino- or carboxy-terminus via a peptide bond to an amino acid sequence of a different peptide. In one embodiment, such a chimeric peptide is
25 produced by recombinant expression of a nucleic acid encoding the protein (comprising a transport receptor-coding sequence joined in-frame to a coding sequence for a different protein). Such a chimeric product can be made by ligating the appropriate nucleic acid sequences encoding the desired
30 amino acid sequences to each other by methods known in the art, in the proper coding frame, and expressing the chimeric product by methods commonly known in the art. Alternatively, such a chimeric product may be made by protein synthetic techniques, e.g., by use of a peptide synthesizer. Chimeric
35 genes comprising portions of GIT transport receptor fused to any heterologous protein-encoding sequences may be constructed. A specific embodiment relates to a chimeric

protein comprising a fragment of GIT transport receptor-binding peptides of at least six amino acids.

In another specific embodiment, the GIT transport receptor-binding peptide derivative is a molecule comprising
5 a region of homology with a GIT transport receptor-binding peptide. By way of example, in various embodiments, a first protein region can be considered "homologous" to a second protein region when the amino acid sequence of the first region is at least 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or
10 95% identical, when compared to any sequence in the second region of an equal number of amino acids as the number contained in the first region or when compared to an aligned sequence of the second region that has been aligned by a computer homology program known in the art. For example, a
15 molecule can comprise one or more regions homologous to a GIT transport receptor-binding peptide domain (see *infra*) or a portion thereof.

The GIT transport receptor-binding proteins and derivatives thereof of the invention can be assayed for
20 binding activity by suitable *in vivo* or *in vitro* assays, e.g., as described in the examples *infra* and/or as will be known to the skilled artisan.

Other specific embodiments of derivatives and analogs are described in the subsection below and examples
25 sections *infra*.

5.2. Motifs/Derivatives of GIT Transport Receptor-Binding Peptides Containing One or More Domains of The Protein

In a specific embodiment, the invention relates to
30 GIT transport receptor-binding peptide derivatives and analogs, in particular GIT transport receptor-binding peptide fragments and derivatives of such fragments, that comprise, or alternatively consist of, one or more domains of a GIT transport receptor-binding peptide. In particular, examples
35 of such domains are identified in the examples *infra*.

5.3. Synthesis of Peptides

The peptides and derivatives of the present invention may be chemically synthesized or synthesized using recombinant DNA techniques.

5

5.3.1. Procedure For Solid Phase Synthesis

Peptides may be prepared chemically by methods that are known in the art. For example, in brief, solid phase peptide synthesis consists of coupling the carboxyl group of
10 the C-terminal amino acid to a resin and successively adding N-alpha protected amino acids. The protecting groups may be any known in the art. Before each new amino acid is added to the growing chain, the protecting group of the previous amino acid added to the chain is removed. The coupling of amino
15 acids to appropriate resins is described by Rivier et al., U.S. Patent No. 4,244,946. Such solid phase syntheses have been described, for example, by Merrifield, 1964, J. Am. Chem. Soc. 85:2149; Vale et al., 1981, Science 213:1394-1397; Marki et al., 1981, J. Am. Chem. Soc. 103:3178 and in U.S.
20 Patent Nos. 4,305,872 and 4,316,891. In a preferred aspect, an automated peptide synthesizer is employed.

By way of example but not limitation, peptides can be synthesized on an Applied Biosystems Inc. ("ABI") model 431A automated peptide synthesizer using the "Fastmoc"
25 synthesis protocol supplied by ABI, which uses 2-(1H-Benzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate ("HBTU") (R. Knorr et al., 1989, Tet. Lett., 30:1927) as coupling agent. Syntheses can be carried out on 0.25 mmol of commercially available
30 4-(2',4'-dimethoxyphenyl)-(9-fluorenyl-methoxycarbonyl)-aminomethyl)-phenoxy polystyrene resin ("Rink resin" from Advanced ChemTech) (H. Rink, 1987, Tet. Lett. 28:3787). Fmoc amino acids (1 mmol) are coupled according to the Fastmoc protocol. The following side chain
35 protected Fmoc amino acid derivatives are used:
FmocArg(Pmc)OH; FmocAsn(Mbh)OH; FmocAsp(^tBu)OH;
FmocCys(Acm)OH; FmocGlu(^tBu)OH; FmocGln(Mbh)OH; FmocHis(Tr)OH;

FmocLys(Boc)OH; FmocSer(^tBu)OH; FmocThr(^tBu)OH;
 FmocTyr(^tBu)OH. [Abbreviations: Ac_m, acetamidomethyl; Boc,
 tert-butoxycarbonyl; ^tBu, tert-butyl; Fmoc,
 9-fluorenylmethoxycarbonyl; Mb_h, 4,4'-dimethoxybenzhydryl;
 5 Pmc, 2,2,5,7,8-pentamethylchroman-6-sulfonyl; Tr, trityl].

Synthesis is carried out using N-methylpyrrolidone
 (NMP) as solvent, with HBTU dissolved in
 N,N-dimethylformamide (DMF). Deprotection of the Fmoc group
 is effected using approximately 20% piperidine in NMP. At
 10 the end of each synthesis the amount of peptide present is
 assayed by ultraviolet spectroscopy. A sample of dry peptide
 resin (about 3-10 mg) is weighed, then 20% piperidine in DMA
 (10 ml) is added. After 30 min sonication, the UV
 (ultraviolet) absorbance of the dibenzofulvene-piperidine
 15 adduct (formed by cleavage of the N-terminal Fmoc group) is
 recorded at 301 nm. Peptide substitution (in mmol g⁻¹) can be
 calculated according to the equation:

$$\text{substitution} = \frac{A \times v}{7800 \times w} \times 1000$$

20 where A is the absorbance at 301 nm, v is the volume of 20%
 piperidine in DMA (in ml), 7800 is the extinction coefficient
 (in mol⁻¹dm³cm⁻¹) of the dibenzofulvene-piperidine adduct, and
 w is the weight of the peptide-resin sample (in mg).

25 Finally, the N-terminal Fmoc group is cleaved using
 20% piperidine in DMA, then acetylated using acetic anhydride
 and pyridine in DMA. The peptide resin is thoroughly washed
 with DMA, CH₂Cl₂, and finally diethyl ether.

30 5.3.2. Cleavage And Deprotection

By way of example but not limitation, cleavage and
 deprotection can be carried out as follows: The air-dried
 peptide resin is treated with ethylmethyl-sulfide (EtSMe),
 ethanedithiol (EDT), and thioanisole (PhSMe) for
 35 approximately 20 min. prior to addition of 95% aqueous
 trifluoroacetic acid (TFA). A total volume of approximately
 50 ml of these reagents per gram of peptide-resin is used.

The following ratio is used: TFA:EtSMe:EDT:PhSMe (10:0.5:0.5:0.5). The mixture is stirred for 3 h at room temperature under an atmosphere of N₂. The mixture is filtered and the resin washed with TFA (2 x 3 ml). The combined filtrate is evaporated in vacuo, and anhydrous diethyl ether added to the yellow/orange residue. The resulting white precipitate is isolated by filtration. See King et al., 1990, Int. J. Peptide Protein Res. 36:255-266 regarding various cleavage methods.

10

5.3.3. Purification of the Peptides

Purification of the synthesized peptides can be carried out by standard methods including chromatography (e.g., ion exchange, affinity, and sizing column chromatography, high performance liquid chromatography (HPLC)), centrifugation, differential solubility, or by any other standard technique.

15

5.3.4. Biological Peptide Libraries

Biological peptide libraries can be used to express and identify peptides that bind to GIT transport receptors. According to this second approach, involving recombinant DNA techniques, peptides can, by way of example, be expressed in biological systems as either soluble fusion proteins or viral capsid proteins.

20

5.3.4.1. Methods To Identify Binders: Construction Of Libraries

In a specific embodiment, the peptides of the invention that specifically bind to GIT transport receptors are identified by screening a random peptide library by contacting the library with a ligand selected from among HPT1, hPEPT1, D2H, or hSI (or a molecule consisting essentially of an extracellular domain thereof or fragment of the domain) to identify members of the library that specifically bind to the ligand.

30

35

In a particular embodiment, a process to identify the peptides of the present method utilizes a library of recombinant vectors constructed by methods well known in the art and comprises screening a library of recombinant vectors
5 expressing inserted synthetic oligonucleotide sequences encoding extracellular GIT transport receptor domains, for example, attached to an accessible surface structural protein of a vector to isolate those members producing peptides that bind to HPT1, hPEPT1, D2H, or hSI. The nucleic acid sequence
10 of the inserted synthetic oligonucleotides of the isolated vector is determined and the amino acid sequence encoded can be deduced to identify a binding domain that binds the ligand of choice (e.g., HPT1, hPEPT1, D2H, or hSI).

The present invention encompasses a method for
15 identifying a peptide which binds to a ligand selected from among HPT1, hPEPT1, D2H, or hSI comprising: screening a library of random peptides with the ligand (or an extracellular domain or fragment thereof) under conditions conducive to ligand binding and isolating the peptide which
20 binds to the ligand. Additionally, the methods of the invention further comprise determining the nucleotide sequence encoding the binding domain of the peptide identified to deduce the amino acid sequence of the binding domain.

25

5.3.4.2. Preparation of Extracellular Domain Ligand

In a specific embodiment, molecules consisting essentially of an extracellular domain of the desired GIT
30 transport receptor or a fragment of an extracellular domain are used to screen a random peptide library for binding thereto. Preferably, a nucleic acid encoding the extracellular domain is cloned and recombinantly expressed, and the domain is then purified for use. The GIT transport
35 receptor is preferably selected from among HPT1, hPEPT1, D2H, or hSI.

5.3.4.3. Methods to Identify Binders: Screening Libraries

Once a suitable random peptide library has been constructed (or otherwise obtained), the library is screened to identify peptides having binding affinity for the GIT transport receptor, e.g., HPT1, hPEPT1, D2H, or hSI. In a preferred aspect, the library is a TSAR library (see U.S. Patent No. 5,498,538 dated March 12, 1996 and PCT Publication WO 94/18318 dated August 18, 1994, both of which are incorporated by reference herein in their entireties). Screening the libraries can be accomplished by any of a variety of methods known to those of skill in the art. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, Adv. Exp. Med. Biol. 251: 215-218; Scott and Smith, 1990, Science 249: 386-390; Fowlkes et al., 1992, BioTechniques 13: 422-427; Oldenburg et al., 1992, Proc. Natl. Acad. Sci. USA 89: 5393-5397; Yu et al., 1994, Cell 76: 933-945; Staudt et al., 1988, Science 241: 577-580; Bock et al., 1992, Nature 355: 564-566; Tuerk et al., 1992, Proc. Natl. Acad. Sci. USA 89: 6988-6992; Ellington et al., 1992, Nature 355: 850-852; U.S. Patent No. 5,096,815, U.S. Patent No. 5,223,409, and U.S. Patent No. 5,198,346, all to Ladner et al.; and Rebar and Pabo, 1993, Science 263: 671-673. See also PCT publication WO 94/18318, dated August 18, 1994.

One of ordinary skill in the art will recognize that, with suitable modifications, the screening methods described below would be suitable for a wide variety of biological expression libraries.

Once a library has been constructed or otherwise obtained, the library is screened to identify binding molecules having specific binding affinity for a ligand for a GIT transport receptor preferably selected from among HPT1, hPEPT1, D2H, or hSI.

Screening the libraries can be accomplished by any of a variety of methods known to those of skill in the art. Exemplary screening methods are described in Fowlkes et al.,

1992, BioTechniques, 13:422-427 and include contacting the vectors with an immobilized target ligand and harvesting those vectors that bind to said ligand. Such useful screening methods, are designated "panning" methods. In
5 panning methods useful to screen the present libraries, the target ligand can be immobilized on plates, beads (such as magnetic beads), sepharose, beads used in columns, etc. If desired, the immobilized target ligand can be "tagged", e.g., using labels such as biotin, fluorescein isothiocyanate,
10 rhodamine, etc. e.g. for FACS sorting. Panning is also disclosed in Parmley, S.F. and Smith, G.P., 1988, Gene 73: 305-318.

In a particular embodiment of the invention, the library can be screened with a recombinant receptor domain.
15 In another embodiment, the library can be screened successively with receptor domains and then on CaCO-2 cells.

For screening of the peptide libraries *in vitro*, the solvent requirements involved in screening are not limited to aqueous solvents; thus, nonphysiological binding
20 interactions and conditions different from those found *in vivo* can be exploited.

Screening a library can be achieved using a method comprising a first "enrichment" step and a second filter lift as follows. The following description is given by way of
25 example, not limitation.

Binders from an expressed library (e.g., in phage) capable of binding to a given ligand ("positives") are initially enriched by one or two cycles of panning or affinity chromatography. A microtiter well is passively
30 coated with the ligand (e.g., about 10 μ g in 100 μ l). The well is then blocked with a solution of BSA to prevent non-specific adherence of the phage of the library to the plastic surface. For example, about 10^{11} phage particles expressing peptides are then added to the well and incubated for several
35 hours. Unbound phage are removed by repeated washing of the plate, and specifically bound phage are eluted using an acidic glycine-HCl solution or other elution buffer. The

eluted phage solution is neutralized with alkali, and amplified, e.g., by infection of *E. coli* and plating on large petri dishes containing Luria broth (LB) in agar. Amplified cultures expressing the binding peptides are then titered and
5 the process repeated. Alternatively, the ligand can be covalently coupled to agarose or acrylamide beads using commercially available activated bead reagents. The phage solution is then simply passed over a small column containing the coupled bead matrix which is then washed extensively and
10 eluted with acid or other eluant. In either case, the goal is to enrich the positives to a frequency of about $> 1/10^5$.

Following enrichment, a filter lift assay is conducted. For example, when specific binders are expressed in phage, approximately $1-2 \times 10^5$ phage are added to 500 μ l of
15 log phase *E. coli* and plated on a large Luria Broth-agarose plate with 0.7% agarose in broth. The agarose is allowed to solidify, and a nitrocellulose filter (e.g., 0.45 μ) is placed on the agarose surface. A series of registration marks is made with a sterile needle to allow re-alignment of
20 the filter and plate following development as described below. Phage plaques are allowed to develop by overnight incubation at 37 °C (the presence of the filter does not inhibit this process). The filter is then removed from the plate with phage from each individual plaque adhered *in situ*.
25 The filter is then exposed to a solution of BSA or other blocking agent for 1-2 hours to prevent non-specific binding of the ligand (or "probe").

The probe itself is labeled, for example, either by biotinylation (using commercial NHS-biotin) or direct enzyme
30 labeling, e.g., with horse radish peroxidase or alkaline phosphatase. Probes labeled in this manner are indefinitely stable and can be re-used several times. The blocked filter is exposed to a solution of probe for several hours to allow the probe to bind *in situ* to any phage on the filter
35 displaying a peptide with significant affinity to the probe. The filter is then washed to remove unbound probe, and then developed by exposure to enzyme substrate solution (in the

case of directly labeled probe) or further exposed to a solution of enzyme-labeled avidin (in the case of biotinylated probe). Positive phage plaques are identified by localized deposition of colored enzymatic cleavage product
5 on the filter which corresponds to plaques on the original plate. The developed filter is simply realigned with the plate using the registration marks, and the "positive" plaques are cored from the agarose to recover the phage. Because of the high density of plaques on the original plate,
10 it may be difficult to isolate a single plaque from the plate on the first pass. Accordingly, phage recovered from the initial core can be re-plated at low density and the process can be repeated to allow isolation of individual plaques and hence single clones of phage.

15 Successful screening experiments are optimally conducted using 3 rounds of serial screening. The recovered cells are then plated at a low density to yield isolated colonies for individual analysis. The individual colonies are selected and used to inoculate LB culture medium
20 containing ampicillin. After overnight culture at 37°C, the cultures are then spun down by centrifugation. Individual cell aliquots are then retested for binding to the target ligand attached to the beads. Binding to other beads having attached thereto a non-relevant ligand, can be used as a
25 negative control.

One aspect of screening the libraries is that of elution. The following discussion is applicable to any system where the random peptide is expressed on a surface fusion molecule. It is conceivable that the conditions that
30 disrupt the peptide-target interactions during recovery of the phage are specific for every given peptide sequence from a plurality of proteins expressed on phage. For example, certain interactions may be disrupted by acid pH but not by basic pH, and vice versa. Thus, it may be desirable to test
35 a variety of elution conditions (including but not limited to pH 2-3, pH 12-13, excess target in competition, detergents, mild protein denaturants, urea, varying temperature, light,

presence or absence of metal ions, chelators, etc.) and compare the primary structures of the binding proteins expressed on the phage recovered for each set of conditions to determine the appropriate elution conditions for each
5 ligand/binding protein combination. Some of these elution conditions may be incompatible with phage infection because they are bactericidal and will need to be removed by dialysis (i.e., dialysis bag, Centricon/Amicon microconcentrators).

In a preferred embodiment, a phage display library
10 of random peptides is screened to select phage expressing peptides that bind to a GIT transport receptor. Preferably, a first step is to isolate a preselected phage library. The "preselected phage library" is a library consisting of a subpopulation of a phage display library. This subpopulation
15 can be formed by initially screening against either a target GIT transport receptor (or domain thereof) so as to permit the selection of a subpopulation of phages which specifically bind to the receptor. Alternatively, the subpopulation can be formed by screening against a target cell or cell type or
20 tissue type or tissue barrier of the gastro-intestinal tract, so as to permit the selection of a subpopulation of phages which either bind specifically to the target cell or target cell type or target tissue or target tissue barrier, or which binds to and/or is transported across (or between) the target
25 cell or target cell type or target tissue or target tissue barrier either *in situ* or *in vivo*. This preselected phage library or subpopulation of selected phages can also be rescreened against the target GIT transport receptor, permitting the further selection of a subpopulation of phages
30 which bind to the GIT transport receptor or target cell or target cell type or target tissue or target tissue barrier or which bind to and/or is transported across the target cell, target tissue or target tissue barrier either *in situ* or *in vivo*. Such rescreening can be repeated from zero to 30 times
35 with each successive "pre-selected phage library" generating additional pre-selected phage libraries.

In a preferred embodiment, a preselected phage library binding a ligand that is a GIT transport receptor preferably selected from among HPT1, hPEPT1, D2H, or hSI is obtained by an *in vitro* screening step as described above, 5 and then the phage are optionally further characterized using *in vitro* assays consisting of binding phage directly to the receptor domain of interest or, alternatively, to Caco-2 cells or using *in vivo* assays. In another preferred embodiment, *in vivo* assays are used that measure uptake of 10 phage by intestinal tissue or, alternatively, through the GIT. In alternative embodiments, such further *in vitro* or *in vivo* assays can be used as the initial screening step.

In vivo assays that may be used are described in the examples *infra*.

15

5.4. Generation of Antibodies to GIT Transport Receptor-Binding Peptides and Derivatives Thereof

According to the invention, a GIT transport receptor-binding peptide, fragments or other derivatives, or 20 analogs thereof, may be used as an immunogen to generate antibodies which immunospecifically bind such an immunogen. Such antibodies include but are not limited to polyclonal, monoclonal, chimeric, single chain, Fab fragments, and an Fab expression library.

25 Various procedures known in the art may be used for the production of polyclonal antibodies to a GIT transport receptor-binding peptide or derivative or analog. For the production of antibody, various host animals can be immunized by injection with the native GIT transport receptor-binding 30 peptides, or a synthetic version, or derivative (e.g., fragment) thereof, including but not limited to rabbits, mice, rats, fowl, etc. Various adjuvants may be used to increase the immunological response, depending on the host species, including but not limited to Freund's (complete and 35 incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet

hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum.

For preparation of monoclonal antibodies directed
5 toward a GIT transport receptor-binding peptide or analog thereof, any technique which provides for the production of antibody molecules by continuous cell lines in culture may be used. For example, the hybridoma technique originally developed by Kohler and Milstein (1975, Nature 256:495-497),
10 as well as the trioma technique, the human B-cell hybridoma technique (Kozbor et al., 1983, Immunology Today 4:72), and the EBV-hybridoma technique to produce human monoclonal antibodies (Cole et al., 1985, in Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc., pp. 77-96). In an
15 additional embodiment of the invention, monoclonal antibodies can be produced in germ-free animals utilizing recent technology (PCT/US90/02545). According to the invention, human antibodies may be used and can be obtained by using human hybridomas (Cote et al., 1983, Proc. Natl. Acad. Sci.
20 U.S.A. 80:2026-2030) or by transforming human B cells with EBV virus *in vitro* (Cole et al., 1985, in Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, pp. 77-96). According to the invention, techniques developed for the production of "chimeric antibodies" (Morrison et al., 1984,
25 Proc. Natl. Acad. Sci. U.S.A. 81:6851-6855; Neuberger et al., 1984, Nature 312:604-608; Takeda et al., 1985, Nature 314:452-454) by splicing the genes from a mouse antibody molecule specific for GIT transport receptor-binding peptides together with genes from a human antibody molecule of
30 appropriate biological activity can be used.

According to the invention, techniques described for the production of single chain antibodies (U.S. Patent 4,946,778) can be adapted to produce GIT transport receptor-binding peptide-specific single chain antibodies. An
35 additional embodiment of the invention utilizes the techniques described for the construction of Fab expression libraries (Huse et al., 1989, Science 246:1275-1281) to allow

rapid and easy identification of monoclonal Fab fragments with the desired specificity for GIT transport receptor-binding peptides, derivatives, or analogs.

Antibody fragments which contain the idiotype of the molecule can be generated by known techniques. For example, such fragments include but are not limited to: the $F(ab')_2$ fragment which can be produced by pepsin digestion of the antibody molecule; the Fab' fragments which can be generated by reducing the disulfide bridges of the $F(ab')_2$ fragment, the Fab fragments which can be generated by treating the antibody molecule with papain and a reducing agent, and Fv fragments.

In the production of antibodies, screening for the desired antibody can be accomplished by techniques known in the art, e.g. ELISA (enzyme-linked immunosorbent assay). For example, to select antibodies which recognize a specific domain of a GIT transport receptor-binding peptide, one may assay generated hybridomas for a product which binds to a GIT transport receptor-binding peptide fragment containing such a domain.

Antibodies specific to a domain of a GIT transport receptor-binding peptide are also provided.

The foregoing antibodies can be used in methods known in the art relating to the localization and activity of the GIT transport receptor-binding peptide sequences of the invention, e.g., for imaging these peptides after *in vivo* administration (e.g., to monitor treatment efficacy), measuring levels thereof in appropriate physiological samples, in diagnostic methods, etc. For instance, antibodies or antibody fragments specific to a domain of a GIT transport receptor-binding peptide or to a derivative of a peptide, such as a dansyl group or some other epitope introduced into the peptide, can be used to 1) identify the presence of the peptide on a nanoparticle or other substrate; 2) quantify the amount of peptide on the nanoparticle; 3) measure the level of the peptide in appropriate physiological samples; 4) perform immunohistology on tissue

samples; 5) image the peptide after *in vivo* administration;
6) purify the peptide from a mixture using an immunoaffinity
column or 7) bind or fix the peptide to the surface of
nanoparticle. This last use envisions attaching the antibody
5 (or fragment of the antibody) to the surface of drug-loaded
nanoparticles or other substrate and then incubating this
conjugate with the peptide. This procedure results in
binding of the peptide in a certain fixed orientation,
resulting in a particle that contains the peptide bound to
10 the antibody in such a way that the peptide is fully active.

Abtides (or Antigen binding peptides) specific to a
domain of a GIT transport receptor-binding peptide or to a
derivative of a peptide, such as a dansyl group or some other
epitope introduced into the peptide, can be used for the same
15 seven purposes identified above for antibodies.

5.5. Assays of GIT Transport Receptor-Binding Peptides, Derivatives and Analogs

The functional activity of GIT transport receptor-
20 binding peptides, derivatives and analogs can be assayed by
various methods.

In a preferred embodiment, in which binding to a
GIT transport receptor is being assayed, the binding can be
assayed by *in vivo* or *in vitro* assays such as described in
the examples *infra*, or by other means that are known in the
25 art.

In another embodiment, where one is assaying for
the ability to bind or compete with full-length GIT transport
receptor-binding peptide for binding to anti-GIT transport
30 receptor-binding peptide antibody, various immunoassays known
in the art can be used, including but not limited to
competitive and non-competitive assay systems using
techniques such as radioimmunoassays, ELISA (enzyme linked
immunosorbent assay), "sandwich" immunoassays,
35 immunoradiometric assays, gel diffusion precipitin reactions,
immunodiffusion assays, *in situ* immunoassays (using colloidal
gold, enzyme or radioisotope labels, for example), western

blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labelled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

Other methods will be known to the skilled artisan and are within the scope of the invention.

15

5.6. Uses

The invention provides compositions comprising the GIT transport receptor-binding proteins of the invention bound to a material comprising an active agent. Such compositions have use in targeting the active agent to the GIT and/or in facilitating transfer through the lumen of the GIT into the systemic circulation. Where the active agent is an imaging agent, such compositions can be administered in vivo to image the GIT (or particular transport receptors thereof). Other active agents include but are not limited to: any drug or antigen or any drug- or antigen-loaded or drug- or antigen-encapsulated nanoparticle, microparticle, liposome, or micellar formulation capable of eliciting a biological response in a human or animal. Examples of drug- or antigen-loaded or drug- or antigen-encapsulated formulations include those in which the active agent is encapsulated or loaded into nano- or microparticles, such as biodegradable nano- or microparticles, and which have the GIT transport receptor-binding protein or derivative or analog adsorbed, coated or covalently bound, such as directly linked or linked via a linking moiety, onto the surface of the nano- or microparticle. Additionally, the protein, derivative or

analog can form the nano- or microparticle itself or the protein, derivative or analog can be covalently attached to the polymer or polymers used in the production of the biodegradable nano- or microparticles or drug-loaded or drug-
5 encapsulated nano- or microparticles or the peptide can be directly conjugated to the active agent. Such conjugations to active agents include fusion proteins in which a DNA sequence coding for the peptide is fused in-frame to the gene or cDNA coding for a therapeutic peptide or protein such that
10 the modified gene codes for a recombinant fusion protein.

In a preferred embodiment, the invention provides for treatment of various diseases and disorders by administration of a therapeutic compound (termed herein "Therapeutic"). Such "Therapeutics" include but are not
15 limited to: GIT transport receptor-binding proteins, and analogs and derivatives (including fragments) thereof (e.g., as described hereinabove) that bind to GIT transport receptors, bound to an active agent of value in the treatment or prevention of a disease or disorder (preferably a
20 mammalian, most preferably human, disease or disorder). Therapeutics also include but are not limited to nucleic acids encoding the GIT transport receptor-binding proteins, analogs, or derivatives bound to such a therapeutic or prophylactic active agent. The active agent is preferably a
25 drug.

Any drug known in the art may be used, depending upon the disease or disorder to be treated or prevented, and the type of subject to which it is to be administered. As used herein, the term "drug" includes, without limitation,
30 any pharmaceutically active agent. Representative drugs include, but are not limited to, peptides or proteins, hormones, analgesics, anti-migraine agents, anti-coagulant agents, anti-emetic agents, cardiovascular agents, anti-hypertensive agents, narcotic antagonists, chelating agents,
35 anti-anginal agents, chemotherapy agents, sedatives, anti-neoplastics, prostaglandins, and antidiuretic agents. Typical drugs include peptides, proteins or hormones such as

insulin, calcitonin, calcitonin gene regulating protein, atrial natriuretic protein, colony stimulating factor, betaseron, erythropoietin (EPO), interferons such as α , β or γ interferon, somatropin, somatotropin, somatostatin, 5 insulin-like growth factor (somatomedins), luteinizing hormone releasing hormone (LHRH), tissue plasminogen activator (TPA), growth hormone releasing hormone (GHRH), oxytocin, estradiol, growth hormones, leuprolide acetate, factor VIII, interleukins such as interleukin-2, and analogs 10 thereof; analgesics such as fentanyl, sufentanil, butorphanol, buprenorphine, levorphanol, morphine, hydromorphone, hydrocodone, oxymorphone, methadone, lidocaine, bupivacaine, diclofenac, naproxen, paverin, and analogs thereof; anti-migraine agents such as heparin, hirudin, and 15 analogs thereof; anti-coagulant agents such as scopolamine, ondansetron, domperidone, etoclopramide, and analogs thereof; cardiovascular agents, anti-hypertensive agents and vasodilators such as diltiazem, clonidine, nifedipine, verapamil, isosorbide-5-mononitrate, organic nitrates, agents 20 used in treatment of heart disorders and analogs thereof; sedatives such as benzodiazepines, phenothiozines and analogs thereof; narcotic antagonists such as naltrexone, naloxone and analogs thereof; chelating agents such as deferoxamine and analogs thereof; anti-diuretic agents such as 25 desmopressin, vasopressin and analogs thereof; anti-anginal agents such as nitroglycerine and analogs thereof; anti-neoplastics such as 5-fluorouracil, bleomycin and analogs thereof; prostaglandins and analogs thereof; and chemotherapy agents such as vincristine and analogs thereof.

30 Representative drugs also include but are not limited to antisense oligonucleotides, genes, gene correcting hybrid oligonucleotides, ribozymes, aptameric oligonucleotides, triple-helix forming oligonucleotides, inhibitors of signal transduction pathways, tyrosine kinase inhibitors and DNA 35 modifying agents. Drugs that can be used also include, without limitation, systems containing gene therapeutics, including viral systems for therapeutic gene delivery such as

adenovirus, adeno-associated virus, retroviruses, herpes simplex virus, sindbus virus, liposomes, cationic lipids, dendrimers, and enzymes. For instance, gene delivery viruses can be modified such that they express the targeting peptide 5 on the surface so as to permit targeted gene delivery.

In a preferred embodiment, a Therapeutic is therapeutically or prophylactically administered to a human patient.

Additional descriptions and sources of Therapeutics 10 that can be used according to the invention are found in various Sections herein.

5.7. Therapeutic/Prophylactic Administration, Compositions and Formulations

15 The invention provides methods of treatment (and prophylaxis) by administration to a subject of an effective amount of a Therapeutic of the invention. In a preferred aspect, the Therapeutic is substantially purified. The subject is preferably an animal, including but not limited to 20 animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably a human.

As will be clear, any disease or disorder of interest amenable to therapy or prophylaxis by providing a 25 drug *in vivo* systemically or by targeting a drug *in vivo* to the GIT (by linkage to a GIT transport-receptor binding protein, derivative or analog of the invention) can be treated or prevented by administration of a Therapeutic of the invention. Such diseases may include but are not limited 30 to hypertension, diabetes, osteoporosis, hemophilia, anemia, cancer, migraine, and angina pectoris, to name but a few.

Any route of administration known in the art may be used, including but not limited to oral, nasal, topical, intravenous, intraperitoneal, intradermal, mucosal, 35 intrathecal, intramuscular, etc. Preferably, administration is oral; in such an embodiment the GIT-transport binding protein, derivative or analog of the invention acts

advantageously to facilitate transport of the therapeutic active agent through the lumen of the GIT into the systemic circulation.

The present invention also provides therapeutic
5 compositions/formulations. In a specific embodiment of the invention, a GIT transport receptor-binding peptide or motif of interest is associated with a therapeutically or prophylactically active agent, preferably a drug or drug-containing nano- or microparticle. More preferably, the
10 active agent is a drug encapsulating or drug loaded nano- or microparticle, such as a biodegradable nano- or microparticle, in which the peptide is physically adsorbed or coated or covalently bonded, such as directly linked or linked via a linking moiety, onto the surface of the nano- or
15 microparticle. Alternatively, the peptide can form the nano- or microparticle itself or can be directly conjugated to the active agent. Such conjugations include fusion proteins in which a DNA sequence coding for the peptide is fused in-frame to the gene or cDNA coding for a therapeutic peptide or
20 protein, such that the modified gene codes for a recombinant fusion protein in which the "targeting" peptide is fused to the therapeutic peptide or protein and where the "targeting" peptide increases the absorption of the fusion protein from the GIT. Preferably the particles range in size from 200-600
25 nm.

Thus, in a specific embodiment, a GIT transport-binding protein is bound to a slow-release (controlled release) device containing a drug. In a specific embodiment, polymeric materials can be used (see Medical Applications of
30 Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J. Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al.,
35 Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J. Neurosurg. 71:105 (1989)).

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a Therapeutic, and a pharmaceutically acceptable carrier. In a specific embodiment, the term

5 "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or

10 vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier

15 when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose,

20 sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying

25 agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides.

30 Oral formulations can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W.

35 Martin. Such compositions will contain a therapeutically effective amount of the Therapeutic, preferably in purified

form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient.

The Therapeutics of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts
5 include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine,
10 triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of the Therapeutic of the invention which will be effective in the treatment of a particular disorder or condition will depend on the nature of the
15 disorder or condition, and can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the
20 seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances.

6. EXAMPLES

25 6.1. Selection of GIT Receptor Targets

The HPT1, hPEPT1, D2H, and hSI receptors were selected for cloning as GIT receptor targets based on several criteria, including: (1) expression on surface of epithelial cells in gastro-intestinal tract (GIT); (2) expression along
30 the length of small intestine (HPT1, hPEPT1, D2H); (3) expression locally at high concentration (hSI); (4) large putative extracellular domains facing into the lumen of the GIT; and (5) extracellular domains that permit easy access and bioadhesion by targeting particles.

35 The four recombinant receptor sites screened with the peptide libraries additionally have the following characteristics:

	<u>Receptor</u>	<u>Characteristics</u>
	D2H	Transport of neutral/basic amino acids; a transport activating protein for a range of amino acid translocases
5	hSI	Metabolism of sucrose and other sugars; represents 9% of brush border membrane protein in Jejunum
	HPT1	di/tri peptide transporter or facilitator of peptide transport
	hPEPT1	di/tri peptide transporter
10	Figures 1-4 (SEQ ID NOS:176, 178, 179, and 181, respectively) show the predicted amino acid sequences for hPEPT1, HPT1, hSI and D2H, respectively.	

15 6.2. Cloning of Extracellular Domain of Selected Receptor Site

The following receptor domains were cloned and expressed as His-tag fusion proteins by standard techniques:

	<u>Receptor</u>	<u>Domain (amino acid residues)</u>
20	hPEPT1 ^a	391-571
	HPT1 ^b	29-273
	hSI ^c	272-667
	D2H ^d	387-685

- 25 ^a Liang et al., 1995, J. Biol. Chem. 270:6456-6463
 ^b Dantzig et al., 1994, Association of Intestinal Peptide Transport with a Protein Related to the Cadherin Superfamily
 ^c Chantret et al., Biochem. J. 285:915-923
 ^d Bertran et al., J. Biol. Chem. 268:14842-14949

30 The receptor proteins were expressed as His-tag fusion proteins and affinity purified under denaturing conditions, using urea or guanidine HCl, utilizing the pET His-tag metal chelate affinity for Ni-NTA Agarose (Hochuli, E., Purification of recombinant proteins with metal chelate adsorbent, Genetic Engineering, Principals and Methods (J.K. Setlow, ed.), Plenum Press, NY, Vol. 12 (1990), pp. 87-98).

35

6.3. Phage Libraries

Three phage DC8, D38, and DC43 libraries expressing N-terminal pIII fusions in M13 were used to identify peptides that bind to the GIT receptors. The D38 and DC43 libraries
5 which are composed of 37 and 43 random amino acid domains, respectively, have been described previously (McConnell et al., 1995, Molecular Diversity, 1:165-176). The DC8 library is similar to the other two except that the random insert is 8 amino acids long flanked on each side by a cysteine residue
10 (i.e., CX₈C).

6.4. Biopanning

Three rounds of biopanning on the GIT receptors were performed generally by standard methods (McConnell et al., 1995, Molecular Diversity, 1:165-176), using a mixture
15 of the DC8 (1×10^{10} pfu), D38 and DC43 (1×10^{11} pfu) phage libraries. After each round of panning the percentage of phage recovered was determined. Following the first two rounds of panning, the eluted phage were amplified overnight.
20 Phage from the third pan were plated out and 100 plaques were picked, amplified overnight and screened in an ELISA assay for binding to the relevant receptor and BSA. After data analysis, phage clones were identified which had high absorbance in the ELISA assay and/or a good ratio of binding
25 to target compared to binding to BSA. The Insulin Degrading Enzyme (IDE) and recombinant human tissue factor (hTF) were used as irrelevant controls. Several variations of the standard panning technique, discussed below, were used. Selection or panning methods followed one of two strategies.
30 The first strategy involved panning the mixed libraries on the specific GIT receptor adsorbed to a solid surface. The second strategy panned the libraries twice against the GIT receptor and then against Caco-2 cells (Peterson and Mooseker, 1992, J. Cell Science 102:581-600). Selection
35 methods are reflected in the clone nomenclature as described below:

S designates the clone was identified by binding to the hS1 receptor domain.

D designates the clone was identified by binding to the D2H receptor domain.

5 P designates the clone was identified by binding to the PEPT1 receptor domain.

H designates the clone was identified by binding to the HPT-1 receptor domain.

Phage designated Ni are from a solid phase band GIT
10 receptor pan that used the standard procedure with the addition of Ni-NTA Agarose (Qiagen, Chatsworth, CA). Receptor coated plates were blocked with 0.5% BSA/PBS containing 160 μ l Ni-NTA agarose and libraries were panned in the presence of 50 μ l Ni-NTA agarose. The receptor proteins
15 were expressed as His-tag fusions. The His-tag has a high affinity for Ni-NTA Agarose. Blocking the plate and panning in the presence of Ni-NTA agarose minimized phage binding to the His-tag portion of the recombinant receptor.

Phage with the designation AX were eluted with acid
20 and Factor Xa. Phage were first eluted by standard acid elution then Factor Xa (New England Biolabs, Beverly, MA: 1 μ g protease in 300 μ l of 20mM Tris-HCL, 100mM NaCl, 2mM CaCl₂) was added to the panning plate and incubated 2 hours. Phage from both elution methods were pooled together then plated.

25 Phage with the designation AB were eluted with acid and base. Phage were eluted first by standard acid elution then 100mM triethylamine pH 12.1 was added to the panning plate for 10 minutes. Phage from both elution methods were pooled together then plated.

30 C designates panning on receptor followed by Caco-2 cells. First and second round pans were performed on the receptor and the third round pan was on snapwells of Caco-2 cells. DCX11, DCX8 and DCX33 were identified by two pans on D2H receptor, third pan on Caco-2 cells. The third round
35 Factor Xa eluate from the Caco-2 cells was screened by ELISA on D2H, BSA and fixed Caco-2 cells. For HCA3 the first two rounds of panning were performed on the HPT-1 receptor and

the third pan was on monolayers cultured on snapwells of Caco-2 cells.

Phage designated 5PAX were carried through five rounds of panning after which a number of phage were 5 sequenced prior to screening by ELISA.

6.5. Sequencing of Selected Phage

The amino acid sequence of phage inserts demonstrating a good ratio of binding to receptor domains 10 and/or Caco-2 cells over background BSA binding were deduced from the nucleotide sequence obtained by sequencing (Sequenase®, U.S. Biochemical Corp., Cleveland, OH) both DNA strands of the appropriate region in the viral genome. The third round acid eluate was screened by ELISA on HPT-1, BSA 15 and Caco-2 fixed cells. Phage designated 5PAX were carried through five rounds of panning after which a number of phages were sequenced prior to screening by ELISA.

One well of a 24 well plate was coated with 10 µg/ml of GIT receptor and the plate was incubated overnight 20 at 4°C. The plate was blocked with 0.5 BSA-PBS for one hour. A mixture of the DC8, D38 and DC43 phage libraries was added to the plate and the plate was incubated for 2 to 3 hours at room temperature on a rotator. After washing the well 10 times with 1% BSA plus 0.05% Tween 20 in PBS, the well was 25 eluted with 0.05M glycine, pH2. The phage was then eluted with 0.2M NaPO₄. The eluted phage was titered on agar plates; the remaining phage was amplified overnight. The next day the amplified phage was added to a second coated plate and the panning procedure was repeated as described above. The 30 eluted phage from the second pan as well as the amplified phage from the first pan was titered on agar plates. Following amplification overnight of the phage from the second pan, the panning procedure was repeated as described above. The phage eluted from the third pan and the amplified 35 phage from the second pan were then titered overnight on agar plates. Isolated phage colonies were amplified overnight prior to use in an ELISA assay.

6.6. Receptor ELISA Procedure

96 well plates were coated overnight with GIT receptor, BSA and, optionally, IDE (insulin degrading enzyme, an irrelevant His-fusion protein) or hTF. The plates were
5 blocked for one hour with 0.5% BSA-PBS. After clarification, the amplified phage were diluted 1:100 in 1% BSA plus 0.05% Tween 20 in PBS and added to the plates. Following incubation of the plates on a rotator for 1 to 2 hours, the plates were washed 5 times with 1% BSA plus 0.05% Tween 20 in
10 PBS. Dilute anti-M13-HRP conjugate (anti-M13 antibody linked to horse radish peroxidase (HRP)) was added to all the wells and the plate was incubated for one hour on a rotator. After the plates were washed 5 times, as described above, TMB substrate was added to the wells. The plates were read at
15 650nm absorbance.

RECEPTOR ELISA RESULTS:

Below are the results of ELISA assays which assessed the binding of phage panned on the hSI receptor to
20 microtiter plates coated with hSI and BSA. Table 1 shows the OD results as well as the ratio of hSI to BSA binding.

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Table 1

PHAGE	hSI	BSA	hSI/BSA
S15	0.478	0.053	9
S21	0.845	0.092	9
S22	0.399	0.061	7
SNi10	0.57	0.051	11
SNi28	0.942	0.113	8
SNi34	0.761	0.115	7
SNi38	0.466	0.076	6
SNi45	0.518	0.056	9
SNiAX2	0.383	0.065	6
SNiAX6	0.369	0.056	7
SNiAX8	0.342	0.068	5
BLANK	0.063	0.042	2

Below are the results of an ELISA which assessed the binding of phage panned on the D2H receptor to microtiter plates coated with D2H and BSA. Table 2 shows the OD results as well as the ratio of D2H to BSA binding.

Table 2

Phage	D2H	BSA	D2H/BSA
DAB3	0.406	0.072	6
DAB7	0.702	0.09	8
DAB10	0.644	0.153	4
DAB18	0.467	0.085	5
DAB24	1.801	0.441	4
DAB30	0.704	0.121	6
DAX15	0.391	0.101	4
DAX23	0.698	0.153	5
DAX24	0.591	0.118	5
DAX27	1.577	0.424	4
BLANK	0.038	0.037	1

Below are the results of an ELISA which assessed the binding of phage panned for two rounds on the D2H receptor followed by a third round pan on Caco-2 snapwells. Binding to fixed Caco-2 cells, D2H and BSA was examined.

Table 3 shows the OD results as well as the ratio of D2H to BSA binding.

Table 3

PHAGE	Caco-2	D2H	BSA	D2H/BSA
DCX8	0.498	0.163	0.063	3
DCX11	0.224	0.222	0.071	3
DCX26	0.114	0.956	0.213	4
DCX33	0.164	0.616	0.103	6
DCX36	0.149	0.293	0.064	5
DCX39	0.121	0.299	0.066	5
DCX42	0.308	0.158	0.065	2
DCX45	0.147	0.336	0.075	4
Blank	0.065	0.043	0.04	1

Below are the results of an ELISA which assessed the binding of phage panned on the hPEPT1 receptor to hPEPT1 and BSA. Table 4 shows the OD results as well as the ratio of hPEPT1 to BSA binding.

Table 4

PHAGE	hPEPT1	BSA	PEPT1/BSA
PAX9	0.312	0.079	4
PAX14	1.102	0.139	8
PAX15	0.301	0.079	4
PAX16	0.648	0.171	4
PAX17	0.514	0.095	5
PAX18	0.416	0.087	5
PAX35	0.474	0.065	7
PAX38	0.292	0.064	5
PAX40	0.461	0.076	6
PAX43	0.345	0.069	5
PAX45	0.419	0.081	5
PAX46	0.429	0.077	6
P31	0.807	0.075	11
P90	1.117	0.107	9
5PAX3	0.173	0.04	4
5PAX5	0.15	0.036	4
5PAX7	0.171	0.037	5
5PAX12	0.227	0.04	6
Blank	0.102	0.039	3

Table 5 shows the results of an ELISA which assessed the binding of phage panned on the HPT-1 receptor to HPT-1 and BSA. The table shows the OD results as well as the ratio of HPT-1 to BSA binding.

5

Table 5

PHAGE	HPT1	BSA	HPT/BSA
HAX9	0.382	0.075	5
HAX40	0.991	0.065	15
HAX42	0.32	0.071	5

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Table 6 shows the results of an ELISA which assessed the binding of phage panned for two rounds on the HPT-1 receptor followed by a third round pan on Caco-2 snapwells. Binding to fixed Caco-2 cells, HPT-1 and BSA was examined. The table shows the OD results as well as the ratio of HPT-1 to BSA binding.

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Table 6

PHAGE	Caco-2	HPT1	BSA	HPT1/BSA
HCA3	0.406	0.048	0.038	1

20

CELL ELISA PROCEDURE

Phage ELISA was used as described above with the following changes. Diluent and wash buffer was PBS containing 1%BSA and 0.05% Tween 20 and plates were washed five times at each wash step. Supernatant of infected bacterial cultures was diluted 1:100 and incubated with protein coated plates for 2-3 hours with mild agitation. Anti-M13 Horseradish peroxidase (HRP) conjugate (Pharmacia, Piscataway, NJ) was diluted 1:8000.

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Fixed Caco-2, C2BBel, and A431 cell plates were prepared by growing cells on tissue culture treated microtiter plates. When cells were confluent, plates were fixed with 10% formaldehyde, washed twice with PBS and stored with 0.5%BSA-PBS at -20°C. On the day of the assay, thawed

35

plates were treated with PBS containing 0.1% phenylhydrazine for one hour at 37°C followed by two PBS washes and blocking for one hour with 0.5%BSA-PBS. The standard ELISA procedure was followed at this point.

- 5 Phage which showed specificity to a GIT receptor was further characterized by ELISA on a variety of recombinant proteins. Phage which continued to exhibit GIT receptor specificity was sequenced.

10

Table 7

TARGET BINDING PHAGE INSERT SEQUENCES:

	<u>hSI</u>	<u>SEQ.</u>	
		<u>ID. NO.</u>	
	S15	1	RSGAYESPDGRGGRSYVGGGGCGNIGRKHNWGLRTASPACWD
	S21	2	SPRSFWPVVSRHESFGISNYLGCGYRTCISGMTKSSPIYPRHS
15	S22	3	SSSSDWGGVPGKVVRERFKGRGCGISITSVLTGKPNPCPEPKAA
	SNi10	4	RVGQCTDSDVRRPWARS CAHQCGAGTRNSHGCITRPLRQASAH
	SNi28	5	SHSGGMNRAYGDVFRELDRWNATSHHTRPTPQLPRGPN
	SNi34	6	SPCGGSWGRFMQGG LFGGRTDGC GAHRNRTSASLEPPSSDY
	SNi38	7	RGAADQRRGWSEN LGLPRVGWDAIAHNSYTFTSRRPRPP
20	SNi45	8	SGGEVSSWGRVNDLCARVSWTGCGTARSARTDNKGFLPKHSSLR
	SNiAX2	9	SDSDGDHYGLRGGVRC SLRDRGCGLALSTVHAGPPSFYPKLSSP
	SNiAX4	10	RSLGNYGVTGTVDVTVLPMPGHANHLGVSSASSSDPPRR
	SNiAX6	11	RTTTAKGCLLGSFGVLSGCSFTPTSPPPHLGYPHPSVN
	SNiAX8	12	SPKLSSVGVMTKVTELPTEGPNAISIPISATLGPRNPLR
25			
	<u>D2H</u>		
	DAB3	13	RWCGAELCNSVTKKFRPGWRDHANPSTHHRTPPPSQSSP
	DAB7	14	RWCGADDPCGASRWGGNSLFGCGLRCSAAQSTPSGRIHSTSTS
	DAB10	15	SKSGEGGDSSRGETGWARVRSHAMTAGRFRWYNQLPSDR
30	DAB18	16	RSSANNCEWKS DWMRRACIARYANSSGPARAVDTKAAP
	DAB24	17	SKWSWSSRWGSPQDKVEKTRAGCGGSPSSTNCHPYTFAPPPQAG
	DAB30	18	SGFWEFSRGLWDGENRKS VRS GCGFRGSSAQGPCVTPATIDKH
	DAX15	19	SESGRCRSVSRWMTTWTQKGGCGSNVSRGSPLDPSHQTHATT
	DAX23	20	REWRFAGPPLDLWAGPSLP SFNASSHPRALRTYWSQRPR
35	DAX24	21	RMEDIKNSGWRDSCRWGD LRP GCGSRQWYPSNMRSSRDYPAGGH
	DAX27	22	SHPWYRHWNHGDFSGSGQSRHTPPESPHPGRPNATI

DCX8	23	RYKHDIGCDAGVDKKSSSVRGCGAHSSPPRAGRGRGTMTVSRL
DCX11	24	SQGSKQCMQYRTGRLTVGSEYGCGMNPARGHATPAYPARLLPRYR
DCX26	25	SGRTTSEISGLWGWGDDRSYGWGNLTPNYIPYRQATNRHRYT
DCX33	26	RWNWTVLPATGGHYWTRSTDYHAINNHRPSIPHQHPTPI
5 DCX36	27	SWSSWNWSSKTTRLGDRATREGCGPSQSDGCPYNGRLTTVKPRT
DCX39	28	SGSLNAWQPRSWVGGAFRSHANNLNPKPTMVTRHPT
DCX42	29	RYSGLSPRDNGPACSQEATLEGCGAQLMSTRRKGRNSRPGWTL
DCX45	30	SVGNDKTSRPVSFYGRVSDLWNASLMPKRTTPSSKRHDDG
10 <u>hPEPT1</u>		
PAX9	31	RWPSVGKYGNGSDTIDVHSNDASTKRSLIYNHRRPLFP
PAX14	32	RTFENDGLGVGRSIQKKSQRWYASHNIRSHFASMSPAGK
PAX15	33	SYCRVKGGGEGGHTDSNLARSGCGKVARTSRLQHINPRATPPSR
PAX16	34	SWTRWGKHTHGGFVNKSPPGKNATSPYTDAQLPSDQGGP
15 PAX17	35	SQVDSFRNSFRWYEPSRALCHGCGKRDSTSTRIHNSPSDSYPTR
PAX18	36	SFLRFQSPRFEDYSRTISRLRNATNPSNVSDAHNNRALA
PAX35	37	RSITDGGINEVDLSSVSNVLENANSHRAYRKHRPTLKRP
PAX38	38	SSKVSSPRDPTVPRKGGNVGYGCGHRSSARMPTSALSSITKCYT
PAX40	39	RASTQGGRGVAPEFGASVLGRGCGSATYYTNSTCKDAMGHNYS
20 PAX43	40	RWCEKHKFTAARCSAGAGFERDASRPQPAHRDNTNRNA
PAX45	41	SFQVYPDHGLERHALDGTGPLYAMPGRWIRARPQNRDRQ
PAX46	42	SRCTDNEQCPDTGTRSRVSNNARYFSSRLLKTHAPHRP
P31	43	SARDSGPAEDGSRAVRLNGVENANTRKSSRSNPRGRRHP
P90	44	SSADAIEKAGSLWGRQNNSGCGSPTKKHLKHNRSQTSSSSH
25 5PAX3	45	RPKNVADAYSSQDGAAAEETSHASNAARKSPKHKLRRP
5PAX5	46	RGSTGTAGGERSGVNLNLTDRDNASGSGFKPWYPSNRGHK
5PAX7	47	RWGWERSPSDYDSMDLGARRYATRTHRAPPVRLKAPLP
5PAX12	48	RGWKCEGSQAAYGDKDIGRSRGCGSITKNNTNHAHPSHGAVAKI
30 <u>HPT-1</u>		
HAX9	49	SREEANWDGYKREMSHRSRFWDATHLSRPRRPANSGDPN
HAX35	50	EWYSWKRSSKSTGLGDTATREGCGPSQSDGCPYNGRLTTVKPRK
HAX40	51	REFAERRLWGCDDLWRLDAEGCGPTPSNRAVKHRKPRPRSPAL
HAX42	52	SDHALGTNLRSDNAKEPGDYNCCGNGNSTGRKVFNRRRPSAIP
35 HCA3	53	RHISEYSFANSHLMGGESKRKGCINGSFSPTCPRSPTPAFRRT
H40	54	SRESGMWGSWWRGHRLNSTGGNANMNASLPDPVSTP
PAX2	55	STPPSREAYSYPVSVDSDSDTNAKHSSHNRLRTRSRPN

Table 8

DNA Sequences for Clones used in in vivo Pan

S15 (SEQ ID NO: 56)

5 TCTCACTCCTCGAGATCCGGCGCTTATGAGAGTCCGGATGGTCGGGGGGGTCGGAGCTATG
TGGGGGGCGGGGGTGGNTGTGGTAACATTGGTCGGAAGCATAACCTGTGGGGGCTGCGTAC
CGCGTCGCCGGCCTGCTGGGACTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

S21 (SEQ ID NO: 57)

TCTCACTCCTCGAGTCCTCGCTCTTTCTGGCCCGTTGTGTCCCGGCATGAGTCGTTTGGGA
10 TCTCTAACTATTGGGNTGTGGTTATCGTACATGTATCTCCGGCAGCATGACTAAGTCTAG
CCCGATTTACCCTCGGCATTCTGTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

S22 (SEQ ID NO: 58)

TCTCACTCCTCGAGTAGTAGCTCCGATTGGGGTGGTGTGCCTGGGAAGGTGGTTAGGGAGC
GCTTTAAGGGGCGCGGTTGTGGTATTTCCATCACCTCCGTGCTCACTGGGAAGCCCAATCC
15 GTGTCCGGAGCCTAAGGCGGCCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

SNI 10 (SEQ ID NO: 59)

TCTCACTCCTCGAGAGTTGGCCAGTGCACGGATTCTGATGTGCGGCGTCCTTGGGCCAGGT
CTTGCGCTCATCAGGGTTGTGGTGCGGGCACTCGCAACTCGCACGGCTGCATCACCCGTCC
TCTCCGCCAGGCTAGCGCTCATTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

20 SNI 28 (SEQ ID NO: 60)

TCTCACTCCTCGAGCCACTCCGGTGGTATGAATAGGGCCTACGGGGATGTGTTTAGGGAGC
TTCGTGATCGGTGGAACGCCACTTCCCACCACACTCGCCCCACCCCTCAGCTCCCCCGTGG
GCCTAATTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

SNI 34 (SEQ ID NO: 61)

25 TCTCACTCCTCGAGTCCGTGCGGGGGGTCGTGGGGGCGTTTTATGCAGGGTGGCCTTTTCG
GCGGTAGGACTGATGGTTGTGGTGGCCATAGAAACCGCACTTCTGCGTCTAGAGCCCC
GAGCAGCGACTACTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

SNI 38 (SEQ ID NO: 62)

TCTCACTCCTCGAGGGGCGCCGCCGATCAGCGGCGGGGTGGTCCGAGAACTTGGGGTTGC
30 CTAGGGTGGGGTGGGACGCCATCGCTCACAATAGCTATACGTTACCTCGCGCCGCCCGCG
CCCCCCTCTAGA

SNI 45 (SEQ ID NO: 63)

TCTCACTCCTCGAGCGGTGGGGAGGTCAGCTCCTGGGGCCGCGTGAATGACCTCTGCGCTA
GGGTGAGTTGGACTGGTTGTGGTACTGCTCGTTCCGCGCGTACCGACAACAAAGGCTTTCT
35 TCCTAAGCACTCGTCACTCCGCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

SNI AX2 (SEQ ID NO: 64)

TCTCACTCCTCGAGTGATAGTGACGGGGATCATTATGGGCTTCGGGGGGGGGTGCGTTGTT
CGCTTCGTGATAGGGGTTGTGGTCTGGCCCTGTCCACCGTCCATGCTGGTCCCCCTCTTT
TTACCCCAAGCTCTCCAGCCCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

SNi AX4 (SEQ ID NO: 65)

5 TCTCACTCCTCGAGGAGCTTGGGTAATTATGGCGTCACCGGGACTGTGGACGTGACGGTTT
TGCCCATGCCTGGCCACGCCAACACCTTGGTGTCTCCTCCGCCTCTAGCTCTGATCCTCC
CGGGCGCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

SNi AX6 (SEQ ID NO: 66)

10 TCTCACTCCTCGAGAACTACGACGGCTAAGGGGTGTCTTCTCGGAAGCTTCGGCGTTCTTA
GTGGGTGCTCATTTACGCCAACCTCTCCACCGCCCCACCTAGGATACCCCCCCCCACTCCGT
CAATTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

SNi AX8 (SEQ ID NO: 67)

15 TCTCACTCCTCGAGCCCGAAGTTGTCCAGCGTGGGTGTTATGACTAAGGTCACGGAGCTGC
CCACGGAGGGGCTAACGCCATTAGTATTCCGATCTCCGCGACCTCGGCCCGCGCAACCC
GCTCCGCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DAB3 (SEQ ID NO: 68)

TCTCACTCCTCGAGGTGGTGCGGCGCTGAGCTGTGCAACTCGGTGACTAAGAAGTTTCGCC
CGGGCTGGCGGGATCACGCCAATCCCTCCACCCATCATCGTACTCCCCGCCCAGCCAGTC
CAGCCCTTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

20 **DAB7 (SEQ ID NO: 69)**

TCTCACTCCTCGAGGTGGTGCGGCGCTGATGACCCGTGTGGTGCCAGTCGTTGGCGGGGGG
GCAACAGCTTTGTTTGGTTGTGGTCTTCGTTGTAGTGCGGCGCAGAGCACCCCGAGTGGCAG
GATCCATTCCACTTCGACCAGCTCTAGAATCGAAGGTGCGCTAGACCTTCGAGA

DAB10 (SEQ ID NO: 70)

25 TCTCACTCCTCGAGTAAGTCCGGGGAGGGGGGTGACAGTAGCAGGGGCGAGACGGGCTGGG
CGAGGGTTCGGTCTCACGCCATGACTGCTGGCCGCTTTCGGTGGTACAACCAGTTGCCCTC
TGATCGGTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DAB18 (SEQ ID NO: 71)

30 TCTCACTCCTCGAGGTGAGCGCCAATAATTGCGAGTGGAAGTCTGATTGGATGCGCAGGG
CCTGTATTGCTCGTTACGCCAACAGTTCGGGGCCCCGCCCCGCGCCGTCGACACTAAGGCCGC
GCCCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DAB24 (SEQ ID NO: 72)

35 TCTCACTCCTCGAGTAAGTGGTCTGGAGTTCGAGGTGGGGCTCCCCGCAGGATAAGGTTG
AGAAGACCAGGGCGGGTGTGGTGGTAGTCCAGCAGCACCAATTGTCACCCCTACACCTT
TGCCCCCCCCCGCAAGCCGGCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DAB30 (SEQ ID NO: 73)

TCTCACTCCTCGAGTGGGTTCTGGGAGTTTAGCAGGGGGCTTTGGGATGGGGAGAACCGTA
AGAGTGTCCGGTCGGGTTGTGGTTTTCTGGGCTCCTCTGCTCAGGGCCCGTGTCCGGTCAC
GCCTGCCACCATTGACAAACACTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

5

DAX15 (SEQ ID NO: 74)

TCTCACTCCTCGAGTGAGAGCGGGCGGTGCCGTAGCGTGAGCCGGTGGATGACGACGTGGC
AGACGCAGAAGGGCGGTTGTGGTTCCAATGTTTCCCGCGGTTGCCCCCTCGACCCCTCTCA
CCAGACCGGGCATGCCACTACTTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

10

DAX23 (SEQ ID NO: 75)

TCTCACTCCTCGAGGGAGTGGAGGTTTGCCGGGCGCCGTTGGACCTGTGGGCGGGTCCGA
GCTTGCCCTCTTTTAACGCCAGTTCCCACCCTCGCGCCCTGCGCACCTATTGGTCCCAGCG
GCCCCGCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DAX24 (SEQ ID NO: 76)

15 TCTCACTCCTCGAGGATGGAGGACATCAAGAACTCGGGGTGGAGGGACTCTTGTAGGTGGG
GTGACCTGAGGCCTGGTTGTGGTAGCCGCCAGTGGTACCCCTCGAATATGCGTTCTAGCAG
AGATTACCCCGCGGGGGGCCACTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DAX27 (SEQ ID NO: 77)

20 TCTCACTCCTCGAGTCATCCGTGGTACAGGCATTGGAACCATGGTGACTTCTCTGGTTCCG
GCCAGTCACGCCACACCCCGCCGAGAGCCCCACCCCGGCCGCTAATGCCACCATTTCT
TAGAATCGAAGGTCGCGCTAGACCTTCGAG

DCX8 (SEQ ID NO: 78)

TCTCACTCCTCGAGATATAAGCACGATATCGGTTGCGATGCTGGGGTTGACAAGAAGTCGT
CGTCTGTGCGTGGTGGTTGTGGTGCTCATTTNGTCGCCACCCCGCGCCGGCCGTGGTCTCG
CGGCACGATGGTTAGCAGGCTTTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

25

DCX11 (SEQ ID NO: 79)

TCTCACTCCTCGAGTCAGGGCTCCAAGCAGTGTATGCAGTACCGCACCGGTCGTTTGACGG
TGGGGTCTGAGTATGGTTGTGGTATGAACCCCGCCCGCCATGCCACGCCCGCTTATCCGGC
GCGCCTGCTGCCACGCTATCGCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

30 DCX26 (SEQ ID NO: 80)

TCTCACTCCTCGAGTGGGCGGACTACTAGTGAGATTTCTGGGCTCTGGGGTTGGGGTGACG
ACCGGAGCGGTTATGGTTGGGGTAACACGCTCCGCCCCAACTACATCCCTTATAGGCAGGC
GACGAACAGGCATCGTTATACGTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DCX33 (SEQ ID NO: 81)

35 TCTCACTCCTCGAGGTGGAATTGGACTGTCTTGCCCGCCACTGGCGGCCATTACTGGACGC
GTTTCGACGGACTATCACGCCATTAAACAATCACAGGCCGAGCATCCCCACCAGCATCCGAC
CCCTATCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DCX36 (SEQ ID NO: 82)

TCTCACTCCTCGAGTTGGTCGTGCGTGAATTGGAGCTCTAAGACTACTCGTCTGGGCGACA
GGGCGACTCGGGAGGGTTGTGGTCCCAGCCAGTCTGATGGCTGTCCTTATAACGGCCGCCT
TACGACCGTCAAGCCTCGCACGTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

5

DCX39 (SEQ ID NO: 83)

TCTCACTCCTCGAGTGGTAGTTTGAACGCATGGCAACCGCGGTCATGGGTGGGGGGCGCGT
TCCGGTCACACGCCAACAATAACTTGAACCCCAAGCCCACCATGGTTACTNGTCACCCTAC
CTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

10 **DCX42 (SEQ ID NO: 84)**

TCTCACTCCTCGAGGTATTTCGGGTTTGTCCCCGCGGGACAACGGTCCCGCTTGTAGTCAGG
AGGCTACCTTGGAGGGTTGTGGTGCGCAGAGGCTGATGTCCACCCGTCGCAAGGGCCGCAA
CTCCCGCCCCGGGTGGACGCTCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DCX45 (SEQ ID NO: 85)15 **TCTCACTCCTCGAGCGTGGGGAATGATAAGACTAGCAGGCCGGTTTCCTTCTACGGGCGCG
TTAGTGATCTGTGGAACGCCAGCTTGATGCCGAAGCGTACTCCCAGCTCGAAGCGCCACGA
TGATGGCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA****PAX2 (SEQ ID NO: 86)**20 **TCTCACTCCTCGAGTACTCCCCCAGTAGGGAGGCGTATAGTAGGCCCTATAGTGTCGATA
GCGATTTCGATACGAACGCCAAGCACAGCTCCCACAACCGCCGTTNTGCGGACGCGCAGCCG
CCCGAACTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA****PAX9 (SEQ ID NO: 87)**25 **TCTCACTCCTCGAGATGGCCTAGTGTGGGTTACAAGGGTAATGGCAGTGACACTATTGATG
TTCACAGCAATGACGCCAGTACTAAGAGGTCCCTCATCTATAACCACCGCCGCCCCNTCTT
TCCCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA****PAX14 (SEQ ID NO: 88)**

TCTCACTCCTCGAGAACGTTTGAGAACGACGGGCTGGGCGTCGGCCGGTCTATTGAGAAGA
AGTCGGATAGGTGGTACGCCAGCCACAACATTTCGTAGCCATTTTCGCGTCCATGTCTCCCGC
TGGTAAGTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

30 **PAX15 (SEQ ID NO: 89)**

TCTCACTCCTCGAGCTATTGTCGGGTAAAGGTGGTGGGGAGGGGGGGGCATACGGATTCCA
ATCTGGCTAGGTTCGGGTGTGGTAAGGTGGCCAGGACCAGCAGGCTTCAGCATATCAACCC
GCGCGCTACCCCCCCTCCCGGTCTAGAATCGAAGGTC

PAX16 (SEQ ID NO: 90)35 **TCTCACTCCTCGAGTTGGACTCGGTGGGGCAAGCACANTCATGGGGGGTTTGTGAACAAGT
CTCCCCCTGGGAAGAACGCCACGAGCCCTACACCGACGCCAGCTGCCAGTGATCAGGG
TCCTCCCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA**

PAX17 (SEQ ID NO: 91)

TCTCACTCCTCGAGTCAGGTTGATTCTGTTTCGTAATAGCTTTCGGTGGTATGAGCCGAGCA
GGGCTCTGTGCCATGGTTGTGGTAAGCGCGACACCTCCACCACTCGTATCCACAATAGCCC
CAGCGACTCCTATCCTACACGCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

5

PAX18 (SEQ ID NO: 92)

TCTCACTCCTCGAGCTTTTTGCGGTTCCAGAGTCCGAGGTTTCGAGGATTACAGTAGGACGA
TCTNTCGGTTGCGCAACGCCACGAACCCGAGTAATGTCTCCGATGCGCACAATAACCGGGC
CTTGGCCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

10 PAX35 (SEQ ID NO: 93)

TCTCACTCCTCGAGGAGCATCACCGACGGGGGCATCAATGAGGTGGACCTGAGTAGTGTGT
CGAACGTTCTTGAGAACGCCAACTCGCATAGGGCCTACAGGAAGCATCGCCCCGACCTTGAA
CGGTCTTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

PAX38 (SEQ ID NO: 94)**15 TCTCACTCCTCGAGTTCGAAGGTGAGCAGCCCCGAGGGATCCGACGGTCCC CGGAAGGGCG
GCAATGTTGATTATGGTTGTGGTCACAGGTCTTCCGCCCCGATGCCTACCTCCGCTCTGTC
GTCGATCACGAAGTGCTACACTTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA****PAX40 (SEQ ID NO: 95)****20 TCTCACTCCTCGAGAGCCAGTANGCAGGGCGGCCGGGTGTTGCCCTGAGTTTGGGGCGA
GCGTTTTGGGTNGTGGTTGTGGTAGCGCCACTTATTACACGAACTCCACCAGCTGCAAGGA
TGCTATGGGCCACAACACTACTCGTCTAGAATCGAAGGTCGCGNTAGACCTTCGAGA****PAX43 (SEQ ID NO: 96)****25 TCTCACTCCTCGAGATGGTGCGAGAAGCACAAAGTTTACGGCTGCGCGTTGCAGCGCGGGG
CGGTTTTGAGAGGGANGCCAGCCGTCCGCCCCAGCCTGCCACCGGGGATAATACCAACCG
TAATGCNTNTAGAATCGAAGGTCGCGCTAGACCTTCGAGA****PAX45 (SEQ ID NO: 97)**

TCTCACTCCTCGAGTTTTTCAGGTGTACCCGGACCATGGTCTGGAGAGGCATGCTTTGGACG
GGACGGGTCCGCTTTACGCCATGCCCGGCCGCTGGATTAGGGCGCGTCCGCAGAACAGGGA
CCGCCAGTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

30 PAX46 (SEQ ID NO: 98)

TCTCACTCCTCGAGCAGGTGTACGGACAACGAGCAGTGCCCCGATACCGGGANTAGGTCTC
GTTCCGTTAGTAACGCCAGGTACTTTTCGAGCAGGTTGCTCAAGACTCACGCCCCCATCG
CCCTTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

P31 (SEQ ID NO: 99)**35 TCTCACTCCTCGAGTGCCAGGGATAGCGGGCCTGCGGAGGATGGGTCCC CGCGCCGTCCGGT
TGAACGGGTTGAGAACGCCAACACTAGGAAGTCCTCCCGCAGTAACCCGCGGGGTAGGCG
CCATCCCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA**

P90 (SEQ ID NO: 100)

TCTCACTCCTCGAGTTCCGCCGATGCGGAGAAGTGTGCGGGCAGTCTGTTGTGGTGGGGTA
GGCAGAACAACTCCGGTTGTGGTTCGCCCACGAAGAAGCATCTGAAGCACCGCAATCGCAG
TCAGACCTCCTCTTCGTCCCCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

5 5PAX3 (SEQ ID NO: 101)

TCTCACTCCTCGAGACCGAAGAACGTGGCCGATGCTTATTCGTCTCAGGACGGGGCGGCGG
CCGAGGAGACGTCTCACGCCAGTAATGCCGCGCGGAAGTCCCCTAAGCACAAGCCCTTGAG
GCGGCCTTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

5PAX5 (SEQ ID NO: 102)

10 TCTCACTCCTCGAGAGGCAGTACGGGGACGGCCGGCGGCGAGCGTTCCGGGGTGCTCAACC
TGCACACCAGGGATAACGCCAGCGGCAGCGGTTTCAAACCGTGGTACCCTTCGAATCGGGG
TCACAAGTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

5PAX7 (SEQ ID NO: 103)

TCTCACTCCTCGAGGTGGGGGTGGGAGAGGAGTCCGTCCGACTACGATTCTGATATGGACT
15 TGGGGGCGAGGAGGTACGCCACCCGCACCCACCGCGCGCCCTCGCGTCTTGAAGGCTCC
CCTGCCCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

5PAX12 (SEQ ID NO: 104)

TCTCACTCCTCGAGGCACTGGAAGTGCGAGGGGCTCTCAGGCTGCCTACGGGGACAAGGATA
TCGGGAGGTCCAGGGTGTGGTTCCATTACAAAGAATAACACTAATCACGCCCATCCTAG
20 CCACGGCGCCGTTGCTAAGATCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

HAX9 (SEQ ID NO: 105)

TCTCACTCCTCGAGCCGCGAGGAGGCGAACTGGGACGGCTATAAGAGGGAGATGAGCCACC
GGAGTCGCTTTTGGGACGCCACCCACCTGTCCCGCCCTCGCCGCCCCGCTAACTCTGGTGA
CCCTAACTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

25 HAX40 (SEQ ID NO: 106)

TCTCACTCNTCGAGAGAGTTTCGCGGAGAGGAGTTGTGGGGGTGTGATGACCTGAGTTGGC
GTCTCGACGCGGAGGGTTGTGGTCCCACTCCGAGCAATCGGGCCGTCAAGCATCGCAAGCC
CCGCCCCACGCTCCCCCGCACTCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

HAX42 (SEQ ID NO: 107)

30 TCTCACTCNTNGAGTGATCACGCGTTGGGGACGAATCTGAGGTCTGACAATGCCAAGGAGC
CGGGTGATTACAACTGTTGTGGTAACGGGAATCTACCGGGCGAAAGGTTTTTAACCGTAG
GCGCCCCCTCCGCCATCCCCANTTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

HCA3 (SEQ ID NO: 108)

TCTCACTCCTCGAGGCATATTTCTGAGTATAGCTTTGCGAATTCCCACTTGATGGGTGGCG
35 AGTCCAAGCGGAAGGGTTGTGGTATTAACGGCTCCTTTTCTCCCACTTGTCCCCGCTCCCC
CACCCCAGCCTTCCGCCGCACCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

H40 (SEQ ID NO: 109)

TCTCACTCCTCGAGCCGGGAGAGCGGGATGTGGGGTAGTTGGTGGCGTGGTCACAGGTTGA
 ATTCCACGGGGGGTAACGCCAACATGAATGCTAGTCTGCCCCCGACCCCCCTGTTTCCAC
 TCCGTCTAGAATCGAAGGTCGCGCTAGACCTTCGAG

5 Peptide Motifs

By comparison of the amino acid sequences of the clones binding GIT receptors, certain sequence similarities or "motifs" were recognized. These motifs can often represent the part of the sequence that is important for binding to the target. Table 9 identifies regions of sequence similarity or sequence motifs (in boldface) that were identified among GIT binding peptides (corresponding SEQ ID NOS. are shown in Table 7).

15

Table 9

PEPT-1	
HPT1	
P31	SARDSGPAEDGSRVRLNGVENAN TRKSSRSNPRGRRHP
PAX9	RWPSVGKNGSDTIDVHSNDAS TKRSLIYNHRRPLFP
HAX42	SDHALGTNLRSDNAKEPGDYNCCGNGN STGRK-VFNRRRPSAIP
PAX2	STPPSREAYSRPYSVSDSDTNAKHSSHN RLRTRSRPN
hSI	
SNi10	RVGQCTDSVRRPWARSCAHQCGAGTRNSHGCITRPLRQASAH
SNi38	RGAA DQRRG WSENGLPRVGWDAIAHNSYTF TSRRPRPP
S15	RSGAYESPDGRGGRSYVGGGGCGNIGRKHN LWGLRTAS PACWD
SNi34	SPCGGSWGRFMQGG LFGGRTD GCGAHRNRTSASLEPPSSDY
D2H	
DAB10	SKSGEGGDSSRGETGWARV RS HAMTAGRFRWYNQLPSDR
DAB30	SGFWEFSRGLWDGENRK SVRS GCGFRGSSAQGPCVTPATIDKH
DCX8	RYKHDIGCDAGVDKKSS SVRGCG-AHSSPP RAGRGRGTMVSRL

30 Phage Binding to Caco-2 Cells

Phage expressing presumed GIT binding peptide inserts were also assayed by ELISA on fixed Caco-2 or C2BBel cells as follows. Cells were plated at 1×10^5 cells/well on 100 μ l culture media and incubated at 30°C in 5% CO₂ overnight. 100 μ l 25% formaldehyde was added to each well for 15 minutes. Contents of the wells were removed by inverting the plate. The plate was then washed 3 times with

DPBS. 0.1% phenylhydrazine DPBS solution was added to each well and incubated for 1 hr at 37°C. The plate was inverted and washed 3 times. The plate was blocked with 0.5% BSA-DPBS for 1 hr at room temperature. The plate was inverted and washed 3 times with 1% BPT (PBS containing 1% BSA and 0.05% Tween20). Phage diluted with 1% BPT was added to wells containing fixed cells. Wells without phage added were used to determine background binding of the HRP conjugate. The plates were incubated 2-3 hours on a rotor at room temperature. Plates were washed as before. Plates were incubated with dilute anti-M13-HRP antibody in 1% BPT for 1 hour at room temperature. Following washing, TMB substrate was added and absorbance of the plates were read at 650 nm. Table 10 shows the relative binding of phage encoding peptides to fixed Caco-2 cells.

Table 10.

20 **Relative binding of phage encoding
 peptides to fixed Caco-2 cells**

	<u>Phage</u>	<u>Fixed Caco-2 cell binding</u>
	SNi10	++
	SNi34	+
25	P31	++
	5PAX5	++
	PAX2	+
	HAX42	+
	DCX8	+++
	DCX11	+
	H1	+
30	M13mpl18	-

In vivo phage selection:

35 Further selection of phage expressing peptides capable of binding to the GIT or transporting the GIT was done as follows. The purified library was resuspended in a

buffer, such as TBS or PBS, and introduced onto one side of a tissue barrier, e.g., injected into the duodenum, jejunum, ileum, colon or other *in vivo* animal site using, for instance, a closed loop model or open loop model. Following
5 injection, samples of bodily fluids located across the tissue barrier, e.g., samples of the portal circulation and/or systemic circulation, were withdrawn at predetermined time points, such as 0 to 90 minutes and/or 2 to 6 hours or more. An aliquot of the withdrawn sample (e.g., blood) was used to
10 directly infect a host, e.g., *E. coli*, in order to confirm the presence of phage. The remaining sample was incubated, e.g., overnight incubation with *E. coli* at 37°C with shaking. The amplified phage present in the culture can be sequenced individually to determine the identity of peptides coded by
15 the phage or, if further enrichment is desired, can be precipitated using PEG, and resuspended in PBS. The phage can then be further precipitated using PEG or used directly for administration to another animal using a closed or open GIT loop model system. Portal or systemic blood samples are
20 collected and the phage transported into such circulation systems is subsequently amplified. In this manner, administration of the phage display library with, if desired, repeat administration of the amplified phage to the GIT of the animal, permitted the selection of phage which was
25 transported from the GIT to the portal and/or systemic circulation of the animal.

If desired, following administration of the phage display library to the tissue barrier (e.g., GIT) of the animal model, the corresponding region of the tissue barrier
30 can be recovered at the end of the procedures given above. This recovered tissue can be washed repeatedly in suitable buffers, e.g., PBS containing protease inhibitors and homogenized in, for example, PBS containing protease inhibitors. The homogenate can be used to infect a host,
35 such as *E. coli*, thus permitting amplification of phages which bind tightly to the tissue barrier (e.g., intestinal tissue). Alternatively, the recovered tissue can be

homogenized in suitable PBS buffers, washed repeatedly and the phage present in the final tissue homogenate can be amplified in *E. coli*. This approach permits amplification (and subsequent identification of the associated peptides) of 5 phages which either bind tightly to the tissue barrier (e.g., intestinal tissue) or which are internalized by the cells of the tissue barrier (e.g., epithelial cells of the intestinal tissue). This selection approach of phage which bind to tissues or which are internalized by tissues can be repeated.

10

**Treatment of animal tissue barriers
in vivo with phage display populations**

The purified phage display library (random or preselected) was diluted to 500 μ l in PBS buffer and injected 15 into the closed (or open) intestinal loop model (e.g., rat, rabbit or other species). At time 0 and at successive time points after injection, a sample of either the portal circulation or systemic circulation was withdrawn. An aliquot of the withdrawn blood was incubated with *E. coli*, 20 followed by plating for phage plaques or for transduction units or for colonies where the phage codes for resistance to antibiotics such as tetracycline. The remainder of the withdrawn blood sample (up to 150 μ l) was incubated with 250 μ l of *E. coli* and 5 ml of LB medium or other suitable 25 growth medium. The *E. coli* cultures were incubated overnight by incubation at 37°C on a shaking platform. Blood samples taken at other time points (such as 15 min, 30 min, 45 min, 60 min, up to 6 hours) were processed in a similar manner, permitting amplification of phages present in the portal or 30 systemic circulation in *E. coli* at these times. Following amplification, the amplified phage was recovered by PEG precipitation and resuspended in PBS buffer or TBS buffer. The titer of the amplified phage, before and after PEG precipitation, was determined. The amplified, PEG 35 precipitated phage was diluted to a known phage titer (generally between 10^8 and 10^{10} phage or plaque forming units (p.f.u.) per ml) and was injected into the GIT of the animal

closed (or open) loop model. Blood samples were collected from portal and/or systemic circulation at various time points and the phage transported into the blood samples were amplified in *E. coli* as given above for the first cycle.

5 Subsequently, the phage was PEG-precipitated, resuspended, titered, diluted and injected into the GIT of the animal closed (or open) loop model. This procedure of phage injection followed by collection of portal and/or systemic blood samples and amplification of phage transported into

10 these blood samples can be repeated, for example, up to 10 times, to permit the selection of phages which are preferentially transported from the GIT into the portal and/or systemic circulation.

15 **6.7. Transport of Phage From Rat Lumen Into the Portal and Systemic Circulation**

Phage from random phage display libraries as well as control phage were injected into the lumen of the rat gastro-intestinal tract (*in situ* rat closed loop model).

20 Blood was collected over time from either the systemic circulation or portal circulation and the number of phage which were transported to the circulation was determined by titering blood samples in *E. coli*.

The phage display libraries used in this study were

25 D38 and DC43 in which gene III codes for random 38-mer and 43-mer peptides, respectively. As a negative control, the identical phage M13mp18, in which gene III does not code for a "random" peptide sequence, was used. Both the library phages D38 and DC43 were prepared from *E. coli*, mixed

30 together, dialyzed against PBS, precipitated using PEG/NaCl and were resuspended in PBS buffer. The M13mp18 control was processed in a similar manner. The titer of each phage sample was determined and the phage samples were diluted in PBS to approximately the same titers prior to injection into

35 the rat closed loop model.

For sampling from the systemic circulation, approximately 15 cm of the duodenum of Wistar rats was tied

off (closed loop model), approximately 0.5ml of phage solution was injected into the closed loop and blood (0.4ml) was sampled from the tail vein at various times. The time points used (in min) were: 0, 15, 30, 45, 60, 90, 120, 180, 5 240 and 300 minutes. For sampling from the portal circulation, the portal vein was catheterized, approximately 15 cm of the duodenum was tied off (closed loop model), 0.5ml of phage solution was injected into the closed loop and blood was sampled from the portal vein catheter at various times.

10 As the portal sampling is delicate, sampling times were restricted to 15, 30, 45 and 60 minutes, where possible. The volume of phage injected into each animal was as follows:

	ANIMALS (15)	VOLUME OF PHAGE INJECTED
15	R1-R3	0.50 ml
	R4	0.43 ml
	R5-R15	0.45 ml

The estimated number of transported phage has been adjusted to account for differences in volume injected into each animal (using 0.5 ml as the standard volume).

To investigate transport into the systemic circulation, animals R1, R2 and R3 received the control phage M13mp18 and animals R4, R5, R6 and R7 received the test phage D38/DC43 mix. To investigate transport into the portal circulation, animals R8, R9 and R10 received the control phage M13mp18 and animals R11, R12, R13 and R14 received the test phage D38/DC43 mix. Animal R15* received the combined phage samples from animals R4-R7 (see Table 11) which were sampled from the systemic circulation on day one, followed by amplification in *E. coli*, PEG precipitation and resuspension in PBS. On subsequent analysis, the titer of this phage was found to be 100 times greater than the other phage samples used for animals R8-R14. Thus, the data presented for animal R15* is adjusted down.

Approximately 0.4 ml of the blood was collected at each time point in each model system. 30 μ l of the collected blood (systemic) was mixed with 100 μ l of the prepared *E. coli* strain K91Kan, incubated at 37°C for 30 min, and
5 plated out for plaque formation using Top Agarose on LB plates. Various negative controls were included in the titering experiments. The following day, the number of plaque forming units was determined. Similarly, 30 μ l of the collected blood (portal) and serial dilutions (1:100, 1:1000)
10 thereof was mixed with 100 μ l of the prepared *E. coli* strain K91Kan, incubated at 37°C for 30 min, and plated out for plaque formation using Top Agarose on LB plates. The following day, the number of plaque forming units was determined.

15 In addition, approximately 300 μ l of the collected blood from each time point (systemic and portal) was incubated with 5ml of prepared *E. coli* strain K91Kan in modified growth media containing 5mM $MgCl_2/MgSO_4$ at 37°C overnight with shaking (to permit phage amplification). The samples were
20 centrifuged and the cell pellet was discarded. Samples of the phage supernatant were collected, serially diluted (10^{-2} , 10^{-4} , 10^{-6} , 10^{-8}) in TBS buffer, and plated for plaques in order to determine the number of plaque forming units present in the amplified phage samples.

25 Furthermore, an aliquot of phage was removed from the "amplified" supernatants obtained from test animals R4-R7 (samples from each time point were used), combined, and precipitated using PEG for two hours. The precipitated phage was resuspended in PBS buffer and was injected into closed
30 loop model of animal R15*, followed by portal sampling.

The number of phage transported from the closed loop model into the systemic circulation is presented in Table 11 hereafter. The number of phage transported from the closed loop model into the portal circulation is presented in
35 Table 12 hereafter. These numbers are corrected for phage input difference and for volume input differences. Clearly, more phage are present in the portal samples than in the

systemic samples, indicative of either hepatic or RES clearance and/or phage instability in the systemic circulation. In addition, the uptake of phage from the GIT into the portal circulation is quite rapid, with substantial number of phages detected within 15 minutes. The results from the portal sampling experiments would also indicate that the kinetics of uptake of phage from the D38/DC43 libraries is quicker than that of the control phage. Thus, there may be preferential uptake of phage coding for random peptide sequences from the GIT into the portal circulation. In the case of animals R13, R14 and R15*, the % of the phage transported into the titered blood sample within the limited time frame (30, 45 and 15 mins, respectively) was estimated as 0.13%, 1.1% and 0.013%, respectively.

15

TABLE 11

NUMBER OF PHAGE TRANSPORTED FROM THE CLOSED
LOOP MODEL INTO THE SYSTEMIC CIRCULATION

20	Time (min)	R1	R2	R3	R4	R5	R6	R7
	0	0	0	0	0	0	0	0
	15	0	1	9	0	0	1	7
	30	2	1	0	0	46	1	11
	45	10	4	2	1	32	0	20
	60	63	19	21	1	114	0	21
	90	104	20	18	3	115	0	22
25	120	94	24	27	0	64	0	6
	180	94	12	23	1	413	0	0
	240	14	1	20	0	36	0	0
	300	1	1	4	2	0	0	0
30	Total number of transported phage	382	83	124	8	820	2	87

Animals R1, R2 and R3 received the control phage M13mp18.

Animals R4, R5, R6 and R7 received the test phage D38/DC43 mix.

Table 12

NUMBER OF PHAGE TRANSPORTED FROM THE CLOSED
LOOP MODEL INTO THE PORTAL CIRCULATION

5	Time (min)	R8	R9	R10	R11	R12	R13	R14	R15*
	15	15	6	3	1	19	231,000	1,000,000	20,000
	30	1	5	26	-	0	60,000	272,000	-
	45	-	1	555	-	1	-	1,240,000	-
	60	-	-	-	-	420,000	-	-	-

10 Animals R8, R9 and R10 received the control phage
M13mp18.

 Animals R11, R12, R13 and R14 received the test
phage D38/DC43 mix.

 Animal R15* received the combined phage samples
15 from animals R4-R7 (see Table 11) which were sampled from the
systemic circulation on day one, followed by PEG
precipitation and resuspension in PBS. On subsequent
analysis, the titer of this phage was found to be 100 times
greater than the other phage samples used for animals R8-R14.
20 Thus, the data measuring phage transport into the portal
circulation for animal R15* is adjusted down.

 These studies demonstrated that both the control
phage and the D38/DC43 phages are transported over time from
the lumen of the GIT into the portal and systemic
25 circulation, as demonstrated by titering the phage
transported to the blood in *E. coli*. More phage were
transported from the test phage samples into the portal
circulation than the corresponding control phage sample. In
addition, the kinetics of transport of the test phage into
30 the portal circulation appeared to exceed that of the control
phage. Phage from the D38/DC43 libraries which appeared in
the systemic circulation of different animals (R4-R7) were
pooled, amplified in *E. coli*, precipitated, and re-applied to
the lumen of the GIT, followed by collection in the portal
35 circulation and titering in *E. coli*. These selected phage
were also transported from the lumen of the GIT into the
portal circulation. This *in situ* loop model may represent an

attractive screening model in which to identify peptide sequences which facilitate transport of phage and particles from the GIT into the circulation.

Using this screening model system, a number of 5 preselected phage libraries now exist, including a one pass systemic phage library from animals R4-R7, a one-pass portal library from animals R11-R14, and a two pass, rapid transport, systemic-portal phage library SP-2 from animal R15*.

10

6.8. Transport of Phage From Preselected Phage Libraries From the Rat Lumen Into the Portal and Systemic Circulation

Four preselected phage libraries, GI-D2H, GI-hSI, GI-HPT1 and GI-hPEPT1, were constructed by pooling phage 15 previously selected by screening random phage display libraries D38 and DC43 using the HPT1, HPEPT1, D2H and hSI receptor or binding sites located in the GIT. The phage pools, preselected phage libraries are shown in Table 13. Note that the sequences for PAX2, HAX1, HAX5, HAX6, HAX10, 20 H10 and HAX44 are the same. Also, the sequence for HAX40 is the same as that for H44. The corresponding SEQ ID NOS. are shown in Table 7.

Table 13

25

PRESELECTED PHAGE LIBRARIES

	<u>D2H</u>	<u>HSI</u>	<u>HPT1</u>	<u>hPEPT1</u>
	DAB3	S15	HAX9	PAX2 (H10)
	DAB7	S21	HAX35	PAX9
	DAB10	S22	HAX40 (H44)	PAX14
	DAB18	SNi10	HAX42	PAX15
30	DAB24	SNi28	HCA3	PAX16
	DAB30	SNi34	HAX1	PAX17
	DAX15	SNi38	HAX5	PAX18
	DAX23	SNi45	HAX6	PAX35
	DAX24	SNiAX2	HAX10	PAX38
	DAX27	SNiAX6	H40	PAX40
	DCX8	SNiAX8	M13mp18	PAX43
35	DCX11	M13mp18		PAX45
	DCX26			PAX46
	DCX33			P31
	DCX36			P90

DCX39
DCX42
DCX45
M13mp18

5PAX3
5PAX5
5PAX7
5PAX12
H40
M13mp18

5

Similar to methods described herein above, these preselected phage libraries together with the negative control phage M13mp18 were injected into the rat closed loop model (6 animals per preselected phage library), blood was collected over time from the portal circulation via the portal vein and, at the termination of the experiment, a systemic blood sample was collected from the tail vein and the intestinal tissue region from the closed loop was collected.

15 In particular, phages selected *in vitro* to each receptor or binding site located in the GIT were amplified in *E. coli*, PEG-precipitated, resuspended in TBS and the titer of each phage sample was determined by plaquing in *E. coli* as described above. Subsequently, an equal number of each phage (8 x 10⁸ phage) for each receptor site was pooled into a preselected phage library together with the negative control phage M13mp18 and each preselected phage library was administered to 6 Wistar rats per library (rats 1-6; GI-D2H, rats 7-12; GI-hSI, rats 13-18; GI-hPEPT1, and rats 19-24; GI-HPT1). Using the *in situ* loop model described above, 0.5 ml of preselected phage library solution was injected into the tied-off portion of the duodenum/jejunum. Blood was collected into heparinized tubes from the portal vein at 0, 15, 30, 45 and 60 minutes. A blood sample was taken from the systemic circulation at the end of the experiment. Similarly, the portion of the duodenum/jejunum used for phage injection was taken at the end of the experiment.

30 Thirty microliters of the collected portal blood (neat and 10⁻², 10⁻⁴, 10⁻⁶ dilutions) was added to 30 μ l *E. coli* K91Kan cells (overnight culture) and incubated at 37°C for 10 min. Subsequently, 3 ml of top agarose was added and the samples were plated for plaques. One hundred microliters of

the collected portal blood was added to 100 μ l of *E. coli* K91Kan. Five milliliters of LB medium was then added and the samples were incubated at 37°C overnight in a rotating microbial incubator. The *E. coli* was removed by
5 centrifugation and the amplified phage supernatant samples were either titered directly or were PEG-precipitated, resuspended in TBS and titered. Following titration of the amplified phage, samples containing phage from each set of animals were combined, adjusting the titer of each sample to
10 the same titer, and were plated for plaques on LB agar plates (22cm² square plates). Either 12,000 or 24,000 phage were plated for plaques.

Thirty microliters of the collected systemic blood (neat and 10⁻², 10⁻⁴, 10⁻⁶ dilutions) was added to *E. coli*
15 K91Kan cells, incubated at 37°C for 10 min. Three ml of top agarose was then added and the samples were plated for plaques. One hundred microliters of the collected systemic blood was added to 100 μ l of *E. coli* K91Kan, incubated at 37°C for 10 min. Five milliliters of LB medium was then added and
20 the samples were incubated at 37°C overnight in a rotating microbial incubator. The *E. coli* was removed by centrifugation and the amplified phage supernatant samples were either titered directly or were PEG-precipitated, resuspended in TBS and titered. Following titration of the
25 amplified phage, samples containing phage from each set of animals were combined, adjusting the titer of each sample to the same titer, and were plated for plaques on LB agar plates (22cm² square plates). Either 12,000 or 24,000 phage were plated for plaques.

30 The intestinal tissue portion used in each closed loop was excised. The tissue was cut into small segments, followed by 3 washings in sterile PBS containing protease inhibitors, and homogenized in an Ultra thorex homogeniser (Int-D samples). Alternatively, the tissue (in PBS
35 supplemented with protease inhibitors) was homogenized in an Ultra Thorex homogenizer, washed 3 times in PBS containing protease inhibitors and resuspended in PBS containing

protease inhibitors (Int-G samples). In each case, serial dilutions (neat and 10^{-2} , 10^{-4} , 10^{-6} dilutions) of the tissue homogenate was titered in *E. coli*. In addition, an aliquot (100 μ l) of the tissue homogenate was added to 100 μ l of
 5 *E. coli* K91Kan, incubated at 37°C for 10 min, followed by addition of 5ml of LB medium and incubation overnight at 37°C in a rotating microbial incubator.

The phage amplified from the portal blood, systemic blood and intestinal tissue was plated for plaques. The
 10 plaques were transferred to Hybond-N Nylon filters, followed by denaturation (1.5M NaCl, 0.5M NaOH), neutralization (0.5M TRIS-HCl, pH7.4, 1.5M NaCl), and washing in 2X SSC buffer. The filters were air-dried, and the DNA was cross-linked to the filter (UV crosslinking: 2min, high setting). The
 15 filters were incubated in pre-hybridization buffer (6X SSC, 5X Denhardt's solution, 0.1% SDS, 20 μ g/ml yeast tRNA) at 40°C-45°C for at least 60 min.

Synthetic oligonucleotides, (22-mers), complimentary to regions coding for the receptor or binding
 20 sites used to create the preselected phage library, were synthesized (see Table 14 below).

Table 14

OLIGONUCLEOTIDES USED IN IN VIVO SCREEN

25	CLONE NAME	OLIGO	SEQ. ID. NO.
	S15	5'TCCGGACTCTCATAAGCGCCGG ³ '	111
	S21	5'ACAACGGGCCAGAAAGAGCGAG ³ '	112
	S22	5'ACACCACCCCAATCGGAGCTAC ³ '	113
	SNi10	5'TCAGAATCCGTGCACTGGCCAA ³ '	114
30	SNi28	5'GCCCTATTCATACCACCGGAGT ³ '	115
	SNi34	5'CATCAGTCCTACCGCCGAAAAG ³ '	116
	SNi38	5'CGTATAGCTATTGTGAGCGATG ³ '	117
	SNi45	5'ACGCGCGGAACGAGCAGTACCA ³ '	118
	SNiAX2	5'CCATAATGATCCCCGTCCTACTAT ³ '	119
35	SNiAX6	5'AGACACCCCTTAGCCGTCGTAG ³ '	120
	SNiAX8	5'AGCTCCGTGACCTTAGTCATAA ³ '	121

	CLONE NAME	OLIGO	SEQ. ID. NO.
	DAB3	5'TGCACAGCTCAGCGCCGCACCA 3'	122
	DAB7	5'ACGGGTCATCAGCGCCGCACCA 3'	123
	DAB10	5'TGTCACCCCCCTCCCCGGA CTT 3'	124
5	DAB18	5'ACTCGCAATTATTGGCGCTCGA 3'	125
	DAB24	5'GTCTTCTCAACCTTATCCTGCG 3'	126
	DAB30	5'AAAGCCCCCTGCTAAACTCCCA 3'	127
	DAX15	5'CTGCGTCTGCCACGTCGTCATC 3'	128
	DAX23	5'GTTAAAAGAGGGCAAGCTCGGA 3'	129
10	DAX24	5'CCGAGTTCTTGATGTCCTCCAT 3'	130
	DAX27	5'TCCAATGCCTGTACCACGGATG 3'	131
	DCX8	5'TCGCAACCGATATCGTGCTTAT ³	132
	DCX11	5'TGCATACACTGCTTGGAGCCCT ³	133
	DCX26	5'GAAATCTCACTAGTAGTCCGCC ³	134
15	DCX33	5'GCGGGCAAGACAGTCCAATTCC ³	135
	DCX36	5'GAGCTCCAATTCCACGACGACC ³	136
	DCX39	5'GGTTGCCATGCGTTCAAACCTAC ³	137
	DCX42	5'TCCCGCGGGGACAAACCCGAAT ³	138
	DCX45	5'CTGCTAGTCTTATCATTCCTCCCA ³	139
20	PAX2	5'CTATCGACACTATAGGGCCTAC ³	140
	PAX9	5'TACCCCTTGTAACCCACACTAGG ³	141
	PAX14	5'TTCTTCTGAATAGACCGGCCGA ³	142
	PAX15	5'CCACCACCCTTAACCCGACAAT ³	143
	PAX16	5'AGGGGGAGACTTGTTTCAAAAC ³	144
25	PAX17	5'CGGCTCATACCACCGAAAGCTA ³	145
	PAX18	5'ATCGTCCTACTGTAATCCTCGA ³	146
	PAX35	5'GACACACTACTCAGGTCCACCT ³	147
	PAX38	5'CCATAATCAACATTGCCGCCCT ³	148
	PAX40	5'CAAAACGCTCGCCCCAAACTCA ³	149
30	PAX43	5'GTAAACTTGTGCTTCTCGCACC ³	150
	PAX45	5'CCATGGTCCGGGTACACCTGAA ³	151
	PAX46	5'GTTACTAACGGAACGAGACCTA ³	152
	P31	5'TGTTGGCGTTCTCAACCCCGTT ³	153
	P90	5'ACAACCGGAGTTGTTCTGCCTA ³	154
35	5PAX3	5'TAAGCATCGGCCACGTTCTTCG ³	155
	5PAX5	5'TTATCCCTGGTGTGCAGGTTGA ³	156

	CLONE NAME	OLIGO	SEQ. ID. NO.
	5PAX7	5'TATCAGAATCGTAGTCGGACGG ³ '	157
	5PAX12	5'CTTTGTAATGGAACCACAACCC ³ '	158
	HAX9	5'CGGTGGCTCATCTCCCTCTTAT ³ '	159
5	HAX35	5'ATCAGACTGGCTGGGACCACAA ³ '	160
	HAX40	5'CACAACCTCCTCTCCGCGAACT ³ '	161
	HAX42	5'AGATTCGTCCCCAACGCGTGAT ³ '	162
	HCA3	5'GGGAATTCGCAAAGCTATACTC ³ '	163
	H40	5'CCCCGTGGAATTCAACCTGTGA ³ '	164
10	M13 (positive)	5'GTCGTCTTTCCAGACGT ³ '	165
	M13 (negative)	5'CTTGCATGCCTGCAGGTCGAC ³ '	166

The oligonucleotides (5pmol) were 5'end labelled with ³²P-ATP and T4 polynucleotide kinase and approximately 2.5pmol of
 15 labelled oligonucleotide was used in hybridization studies. Hybridizations were performed at 40-45°C overnight in buffer containing 6X SSC, 5X Denhardt's solution, 0.1% SDS, 20µg/ml yeast tRNA and the radiolabeled synthetic oligonucleotide, followed by washings (20-30 min at 40-45°C) in the following
 20 buffers: (i) 2X SSC / 0.1% SDS, (ii) 1X SSC / 0.1% SDS, (iii) 0.1X SSC / 0.1% SDS. The filters were air-dried and exposed for autoradiography for 15 hours, 24 hours or 72 hours.

Hybridization data indicated that all the
 25 oligonucleotide probes bound specifically to their phage target except for the HAX9 probe which apparently was not labeled. A negative control probe that hybridized only to M13mp18 DNA showed a weak to negative signal in all samples tested (data not shown).

Hybridization data for pools from each receptor
 30 group of rats was compiled. Tables 15, 16, 17 and 18 show a representative compilation of autoradiograph signals of the HSI, D2H, HPT1 and hPEPT1 receptor groups. These Tables show the phage absorption and uptake from the closed loop GIT model to portal and systemic circulation and phage
 35 absorption/internalization to intestinal tissue. In these Tables, Int-G refers to intestinal tissue homogenized prior

to washing and recovery while Int-D refers to intestinal tissue washed prior to homogenization and phage recovery. In all cases, leading phage candidates were present in more than one animal.

5

Table 15

SUMMARY OF AUTORADIOGRAPH SIGNALS OF HSI ANIMAL STUDY

10

15

20

Phage	Portal	Int.-G	Int.-D
S15	++	+/-	+/-
S21	-	-	-
S22	-	-/+	-
SNi-10	+++ / +	++	++
SNi-28	-	-	-
SNi-34	++	-	-
SNi-38	++	-	-
SNi-45	-	-	-
SNiAX-2	-	-	-
SNiAX-6	-	-	-
SNiAX-8	-	-	-
M13	++++++	++++++	++++++
M13	nd*	+	-

*not detected

25

30

35

Table 16

SUMMARY OF AUTORADIOGRAPH SIGNALS OF D2H ANIMAL STUDY

	Phage	Portal	Int.-G	Int.-D
5	DAB3	+++	+/-	-/+
	DAB7	++	++	-/+
	DAB10	++++++	+/-	-/+
	DAB18	-	-	-
	DAB24	-	-	-
	DAB30	++++	++	+++
	DAX15	-	-	-
10	DAX23	-/+	+	-/+
	DAX24	-	-	-
	DAX27	-	+	-
	DCX8	+++++	+/-	-
	DCX11	++++++	++	-/+
	DCX26	-	-	-
	DCX33	+++	++	++
	DCX36	-	-	-
15	DCX39	-	-/+	-
	DCX42	-	-	-/+
	DCX45	-	++	-
	M13 (+)	+++++	+++++	+++++
	M13 (-)	+/-	-/+	-

20

Table 17

SUMMARY OF AUTORADIOGRAPH SIGNALS OF HPT1 ANIMAL STUDY

	Phage	Int.-G	Portal	Systemic
25	H40	-	-	++++
	HAX9	ND	ND	ND
	HAX35	-	+	-
	HAX40	-	-	-
	HAX42	-	++	++
	HCA3	-	-	-
	PAX2	-	+++	++++
	M13 (+)	++++++	++++++	++++++
30	M13 (-)	-	--/+	-

35

Table 18

SUMMARY OF AUTORADIOGRAPH SIGNALS OF hPEPT1 ANIMAL STUDY

	Phage	Int.-G	Portal	Systemic
5	PAX2	-	++	-
	PAX9	++	+++	-
	PAX14	-	++	-
	PAX15	-/+	-	-
	PAX16	-	-	-
	PAX17	+	++/+	-
	PAX18	-	-	-
10	PAX35	-	-	-
	PAX38	-/+	-	-
	PAX40	+	+++	-
	PAX43	+	-	-
	PAX45	-	-	-
	PAX46	-	+++	-
	P31	++	++++	++
15	5PAX3	++/+	++	-
	5PAX5	-	-	++
	5PAX7	+++	-	-
	5PAX12	++++	++	-
	H40	++	++	-
	M13(+)	++++++	++++++	++++++
	M13(-)	-	-	-

20

Apart from the synthetic oligonucleotide to HAX9, all oligonucleotides were initially confirmed to be radiolabeled, as determined by hybridization to the corresponding phage target (eg., phage S15 hybridized to the oligonucleotide S15). In addition, under the experimental conditions used, the oligonucleotides essentially did not hybridize to the negative control phage template M13mp18. Two oligonucleotides were synthesized to the phage M13mp18: (1) a positive oligonucleotide which hybridizes to a conserved sequence in both M13mp18 and each of the GIT receptor or GIT binding site selected phages [designated M13 (positive)]; and (2) a negative oligonucleotide which only hybridizes to a sequence unique to the multiple cloning site of phage M13mp18 and which does not hybridize to any of the GIT receptor or GIT binding site selected phages.

In the case of the hSI pool of phages, only four phages were transported from the closed loop model into the portal circulation: phages S15, SNI-10, SNI-34 and SNI-38. The other phages, S21, S22, SNI-28, SNI-45, SNIAX-2, SNIAX-6 and 5 SNIAX-8, were not transported from the GIT into the portal circulation. In addition, phages SNI-10 and to a lesser extent phages S15 and S22 were found in the intestine samples or fractions, whereas the other phages were not. There was a very low presence (<0.1%) of the phage M13mp18 in the Int-G 10 samples. These results show that phages can be further selected from pre-selected libraries, permitting the identification of phages which are transported from the GIT closed loop into the portal circulation or phages which bind to or are internalized by intestinal tissue.

15 In the case of the D2H pool of phages, there was a rank order by which phages were transported from the GIT closed loop model into the portal circulation, with phages DCX11 and DAB10 preferably transported, followed by phages DCX8, DAB30, DAB3 and DAB7. A number of phages from this pool were not 20 transported into the portal circulation, including phages DAB18, DAB24, DAX15, DAX24, DAX27, DCX26, DCX36, DCX39, DCX42, DCX45. There is a very low level of transport of phage DAX23 from the GIT into the portal circulation. Similarly, only some of the phages were found in the intestinal samples 25 fractions, including phages DAB30, DCX33, DAB7, DCX11, DCX45 and to a much lesser extent phages DAB3, DAB10, DCX8, DCX39, DCX42. Some phages were not found in the intestinal samples, including phages DAB18, DAB24, DAX15, DAX24, DCX26, and DCX36. There was a very low presence (<0.1%) of the phage 30 M13mp18 in the Int-G samples. These results showed that phages can be further selected from pre-selected libraries, permitting the identification of phages which are transported from the GIT closed loop into the portal circulation or phages which bind to or are internalized by intestinal 35 tissue.

In the case of the HPT1 pool of phages, there was a rank order by which phages were transported from the GIT closed

loop model into the portal or systemic circulation. Phage PAX2 (which was used at a 4X concentration relative to the other phages in this pool) followed by phage HAX42 was found in the portal and systemic circulation; phage H40 was found 5 in the systemic circulation only. None of the phages in this pool were found in the intestine samples or fractions. Phage M13mp18 was not found in the intestine fractions or systemic circulation, with very low incidence (<0.001%) in the portal circulation. These results show that phages can be further 10 selected from pre-selected libraries, permitting the identification of phages which are transported from the GIT closed loop into the portal and/or systemic circulation or phages which bind to or are internalized by intestinal tissue.

15 In the case of the hPEPT1 pool of phages, the phages PAX2 and H40 were also included in this pool. A number of phages from this pool were found in the portal circulation, including phages P31 (SEQ ID NO:43), PAX46, PAX9, H40, PAX17, PAX40, PAX2, PAX14, 5PAX3 and 5PAX12. A number of phages 20 were not found in the portal blood including the negative control phage M13mp18, PAX15, PAX16, PAX18, PAX35, PAX38, PAX43, PAX45, P90, 5PAX5 and 5PAX7. The only phage found in the systemic circulation were phages 5PAX5 and P31 (SEQ ID NO:43). In addition, there was preferential binding of some 25 phages to the intestine, including phages 5PAX12, 5PAX7, 5PAX3, H40, P31 (SEQ ID NO:43), PAX9, and to a lesser extent phages PAX38 and PAX15. Some phages were not found in the intestine samples, including the negative control phage M13mp18 and the phages PAX2, PAX14, PAX16, PAX18, PAX35, 30 PAX45, PAX46, P90 and 5PAX5. These results show that phages can be further selected from pre-selected libraries, permitting the identification of phages which are transported from the GIT closed loop into the portal and/or systemic circulation or phages which bind to or are internalized by 35 intestinal tissue.

Further Characterization of Select Sequences

Following initial screening of the four recombinant receptor sites (hPEPT1, HPT1, D2H, hSI) of the gastrointestinal tissue, with the phage display libraries, a series of phage were isolated which showed preferential binding to the respective target receptor sites in comparison to negative control protein BSA protein and the recombinant protein recombinant human tissue factor (hTF) (which, like the recombinant receptors of the gastrointestinal tissue, contained a poly-histidine tag at its NH₂-terminal end). In subsequent experiments same titers of the selected phage which bound to each target receptor site were combined into a single pool (i.e., one pool of HPT1 binding phage, one pool of hPEPT1 binding phage, one pool of D2H binding phage, and one pool of hSI binding phage). Each pool was supplemented with an equivalent titer of the negative control phage M13mp18. These phage pools were injected into a closed duodenal loop region of rat intestinal tissue and subsequently phage was harvested and recovered which was bound to and retained by the intestinal tissue and/or was absorbed from the intestinal loop into the portal and/or systemic circulation. In addition, a selection of the initial phages which bound to the target recombinant receptor site were analyzed for binding to either fixed Caco-2 cells and/or to fixed C2BBel cells. The selection of the final lead peptide sequences was based on the ability of the phage, coding for that peptide sequence (1) to bind to the target recombinant receptor site *in vitro* in preference to its binding to the negative control proteins BSA and/or hTFs, (2) to bind to rat intestinal tissue following injection into a closed duodenal loop of rat intestinal tissue in preference to the negative control phage M13mp18, (3) to be absorbed from rat intestinal tissue into either the portal and/or systemic circulation following injection into a closed duodenal loop of rat intestinal tissue in preference to the negative control phage M13mp18, and (4) to bind to either fixed Caco-2 cells or fixed C2BBel cells in phage binding

studies in preference to the negative control phage M13mp18. Peptides were also selected with consideration to the ease of chemical synthesis.

5 **6.9. GST Fusion Proteins of GIT Targeting Peptides**
 Construction of GST Fusion Proteins of GI
 Targeting Peptides

 Glutathione S-transferase (GST) vectors encoding fusion proteins of GI targeting peptides were constructed in the vector pGEX4T-2 (source, Pharmacia Biotech, Piscataway, NJ). Briefly, single-strand DNA from the clones of interest were amplified by the polymerase chain reaction. The amplified DNA was then cleaved with the restriction enzymes XhoI and NotI and then ligated into SalI/NotI cleaved pGEX4T-2. Following transformation, the DNA sequence for each construct was verified by sequencing.

 For construction of the truncated versions of the GST fusion proteins, where the inserted sequence was less than 45 base pairs, overlapping oligonucleotides containing cohesive SalI and NotI termini, and encoding the sequence of interest, were annealed and then ligated directly into SalI/NotI cleaved pGEX4T-2. Following transformation, the DNA sequence for each construct was verified.

 A diagrammatic representation of the various GST fusion protein constructs that have been synthesized is indicated in Figures 5A-5C.

Expression and Purification of GST Fusion Proteins

Escherichia coli BL21 cells containing GST fusion protein constructs were grown overnight in 2X YT media containing 100 µg/ml ampicillin (2X YT/amp). Overnight cultures were diluted 1:100 in 2X YT broth (100 ml), and cells were grown to an A₆₀₀ of 0.5 at 30°C, induced with 1mM isopropyl-1-thio-B-D-galactopyranoside, and grown for an additional 3 h. Cells were harvested by centrifugation and resuspended in 5 ml of PBS containing a mixture of the proteinase inhibitors (Boehringer/Mannheim). Cells were

sonicated on ice, and the cell lysates were centrifuged at 12,000 x g for 10 minutes at 4°C. Supernatant fractions were reacted for 30 minutes at room temperature with 2 ml of a 50% slurry of glutathione-Sepharose® 4B, washed 3 times with 1.5 ml of PBS (at room temperature), and the bound GST fusion proteins were eluted by reaction for 10 minutes at room temperature with 3 X 1ml of 10 mM reduced glutathione in 50 mM Tris HCl pH 8.0. Protein was quantified by the Bio-Rad protein assay followed by characterization by SDS-10 polyacrylamide gel electrophoresis.

ELISA of GST fusion peptides

The standard ELISA procedure was modified as follows. GST proteins were diluted to an appropriate 15 concentration in PBS containing 1%BSA and 0.05% Tween20 (1%BPT), titered and incubated one hour at room temperature. Following five washes an anti-GST monoclonal antibody was added (Sigma, St. Louis Clone GST-2 diluted 1:10,000 in 1%BPT) and incubated one hour. After five more washes goat 20 anti-mouse IgG2b-HRP was added (Southern Biotechnology Associates Inc., Birmingham, AL, diluted 1:4000 in 1%BPT) and incubated one hour. After five washes plates were developed with TMB peroxidase substrate (Kirkegard and Perry, Gaithersburg, MD). All data is presented with background 25 binding subtracted.

Figure 6 shows the binding of GST-SNi10, GST-SNi34 and GST alone to the hSI receptor and to fixed C2BBel cells.

GST Fusion Proteins of Selected GIT Targeting Peptides

30 Results show that GST-DXB8, GST-PAX2, GST-P31, GST-SNi10 and GST-SNi34 bound fixed Caco-2 or C2BBel cells (Figures 7 and 8) relative to GST control binding. GST-HAX42, GST-5PAX5, all showed weak to moderate binding relative to GST control.

35 Interestingly, P31 truncation 103-GST fusion protein bound almost as well as full-length P31 (SEQ ID NO:43) to fixed Caco-2 cells (A). This suggests the portion

of the P31 sequence (SEQ ID NO:43) responsible for binding resides in this portion. PAX2.107 bound similarly to full-length PAX2; therefore, this portion most likely contains the amino acid sequence responsible for binding (B). In preliminary assays, none of the DCX8 truncations bound similarly to full-length DCX8 to Caco-2 cells suggesting the binding region spans more than one of these pieces.

Inhibition of Binding by Synthetic Peptides

10 Binding of GST-P31 to fixed C2BBel Cells

The standard ELISA procedure was modified as follows. GST fusion proteins and peptides were diluted to an appropriate concentration in PBS containing 1% BSA and 0.05% Tween 20. Peptides were titered, a constant concentration of diluted GST protein was added to titered peptides and the mixture was incubated one hour at room temperature. Following five washes, an anti-GST monoclonal antibody was added (Sigma, St. Louis Clone GST-2 diluted 1:10,000 in 1% BPT) and incubated one hour. After five more washes goat anti-mouse IgG2b-HRP was added (Southern Biotechnology Associates Inc., Birmingham, AL, diluted 1:4000 in 1% BPT) and incubated one hour. After five washes plates were developed with TMB peroxidase substrate (Kirkegard and Perry, Gaithersburg, MD). All data is presented with background binding subtracted.

Figures 9A and 9B show the inhibition of GST-P31 binding to C2BBel fixed cells. The peptide competitors are ZElan024 which is the dansylated peptide version of P31 (SEQ ID NO:43) and ZElan044, ZElan049 and ZElan050 which are truncated, dansylated pieces of P31 (SEQ ID NO:43). Data is presented as O.D. vs. peptide concentration and as percent inhibition of GST-P31 binding vs. peptide concentration. Uncompeted GST-P31 binding was considered as 100% binding. IC₅₀ values are estimates using the 50% line on the percent inhibition graph.

GST-P31 and GST-PAX2 exhibited no crossreactive binding to ZElan024 (P31) (SEQ ID NO:43) and ZElan018 (PAX2)

at the 0.5 $\mu\text{g/ml}$ concentration used in competition assays. GST-HAX42 exhibited crossreactivity to ZElan018 (PAX2) and ZElan021 (HAX42) at the 5 $\mu\text{g/ml}$ concentration used in competition assays.

5 Figures 10A-10C present a compilation of data generated by competition ELISA of GST-P31, GST-PAX2, GST-SNi10 and GST-HAX42 versus various dansylated peptides on fixed C2BBel cells. IC_{50} values are in μM and include ranges determined from multiple assays. The GST/C2BBel column is a
10 summary of GST protein binding to fixed C2BBel cells.

Binding to fixed Caco-2 Cells

Caco-2 cells were fixed, treated with phenylhydrazine and blocked as described above. Synthetic
15 peptides (100 $\mu\text{g/ml}$) were applied in duplicate to Caco-2 cells and serially diluted down the 96-well plate. The corresponding GST-peptide fusion protein (10 μg) was added to each well and the plates were incubated for 2h at room temperature with agitation. Binding of the GST-peptide
20 fusion proteins to the cells was assayed using the ELISA technique described above. GST-P31 binding was inhibited by ZElan024, ZElan028 and ZElan031 as well as the two D forms ZElan053 and ZElan054. GST-PAX2 binding was inhibited by ZElan032, ZElan033, and ZElan035. GST-HAX42 binding was not
25 inhibited by ZElan021 (full length HAX42) but it was inhibited by ZElan018 (PAX2) and ZElan026 and ZElan038 (scrambled PAX2 peptides).

Transport and Uptake of GST-Peptide Fusions into Live Caco-2 Cells

30 Transport and uptake of GST-peptide fusions and deletion derivatives across cultured polarized Caco-2 monolayers over 4 hours in HBSS buffer was examined using an anti-GST ELISA assay. In another experiment, transport and
35 uptake of GST-peptide fusions and deletion derivatives across

cultured polarized Caco-2 monolayers over 24 hours in serum-free medium (SFM) was examined using an anti-GST ELISA assay.

Materials

- 5 Buffered Hank's balanced salt solution (bHBSS) = 1x HBSS (Gibco CN.14065-031) supplemented with 0.011M glucose (1g/l), 25 mM Hepes (15 mM acid (3.575g/l; Sigma CN.H3375); 10mM base (2.603g/l; Sigma CN.H1016)).

Chloroquine: Made up as 10mM solution in water

- 10 [Sigma CN C6628]

Lysate buffer: 30 mM Tris-HCl pH8.0; 1mM EDTA

Serum-free medium (SFM) is normal medium without serum.

15 Method

- a) 4h HBSS study: Transepithelial electrical flux (TER) across the Caco-2 monolayers grown on snapwells (passage 33; 23 days old) was measured to confirm monolayer integrity before beginning the experiment. The medium was
20 removed and the cells were washed once with bHBSS. bHBSS containing 100 μ M chloroquine was added and the cells were incubated for 2h at 37°C. The bHBSS+chloroquine was replaced with 0.5ml bHBSS containing GST-peptide fusions (100 μ g/ml) and the cells were incubated as before. Basolateral samples
25 were removed at the following times: 0, 0.5h, 2h, and 4h. At 4h, TER was measured, the apical medium was sampled and the apical reservoir was washed 6 times with HBSS. The cells were allowed to lyse for 1h on ice in lysate buffer, after which, lysate sample was collected. All samples were stored
30 at -70°C until assay by anti-GST ELISA. Before analysis, samples were normalized for protein content relative to each other using a BioRad protein assay.

- b) 24h SFM study: Transepithelial electrical flux (TER) across the Caco-2 monolayers grown on snapwells
35 (passage 33; 23 days old) was measured to confirm monolayer integrity before beginning the experiment. The medium was removed and the cells were washed once with SFM. SFM

containing GST-peptide fusions (100µg/ml) was added to the cells which were incubated at 37°C for 24h at 5% CO₂. After 24 hours, TER readings were taken, and samples from the basolateral and apical reservoirs were removed. The apical
5 reservoir was washed 6 times with PBS. The cells were allowed to lyse for 1h on ice in lysate buffer, after which lysate sample was collected. All samples were stored at -70° until assay by anti-GST ELISA. Before analysis, samples were normalized for protein content relative to each other using a
10 BioRad protein assay.

Results

All of the GST-peptide fusions and controls examined were transported across live Caco-2 monolayers.
15 Full-length GST-P31 and GST-DCX8, but not truncations of these molecules had a higher flux than GST alone.

Internalization of GST-peptide fusions into polarized Caco-2 cells was investigated in two experiments. In experiment 1, 15µg of GST-peptide fusion was applied in
20 bHBSS and internalized GST-peptide was recovered by lysing the cells after 4h. In experiment 2, 10µg of GST-peptide was applied in either a) bHBSS (lysate recovered after 4h), or b) serum-free medium (lysate recovered after 24h).

Figure 11A describes complete transport of GST-peptide across a polarized Caco-2 monolayer and does not necessarily refer to internalization, i.e., the GST-peptide was recovered from the basolateral reservoir of a snapwell but the proteins could have crossed the barrier by the paracellular route.

30

Effect of Thrombin Cleavage on Binding of GST-Peptide Fusions to Fixed Caco-2 Cells

Binding of intact and thrombin-cleaved GST-peptide fusions to fixed Caco-2 cells was compared. Reduced binding
35 of the thrombin-cleaved GST-peptide fusions relative to intact fusions indicates that the peptide component of the fusion, and not the GST domain, mediates binding.

Method

Confluent Caco-2 monolayers grown in 96-well plates (p38) were fixed and treated with 0.1% phenylhydrazine before blocking with 0.1% BSA in PBS. Thirty micrograms of each GST-peptide was treated with bovine thrombin (1 μ /ml; 0.4 NIH units; Sigma CN.T9681) for 18h at room temperature in 20mM Tris-HCl pH8.0, 150mM NaCl, 2.5mM CaCl₂. Controls were similarly treated without addition of thrombin. Ten micrograms of each GST-peptide fusion was removed for PAGE analysis, and 10 μ g of fusions were added in duplicate to the fixed Caco-2 cells before 5-fold serial dilutions (1% BPT diluent). The fusions were allowed to bind for 1h at room temperature. Following 6 washes with 1% BPT, binding was assayed by ELISA.

15

Results

Results are shown in Figure 12.

Conclusions:

PAGE analysis confirmed that the GST-peptide fusions were effectively cleaved with thrombin. Cleavage with thrombin significantly reduced detection of binding of GST-P31.103, GST-PAX2.106, GST-DCX8, GST-SNi10 to fixed Caco-2 cells, indicating that the peptide component, and not the GST domain, mediates binding.

6.10. Synthesis of Peptides

6.10.1. Procedure For Solid Phase Synthesis

Peptides may be prepared by methods that are known in the art. For example, in brief, solid phase peptide synthesis consists of coupling the carboxyl group of the C-terminal amino acid to a resin and successively adding N-alpha protected amino acids. The protecting groups may be any known in the art. Before each new amino acid is added to the growing chain, the protecting group of the previous amino acid added to the chain is removed. The coupling of amino acids to appropriate resins is described by Rivier et al.,

U.S. Patent No. 4,244,946. Such solid phase syntheses have been described, for example, by Merrifield, 1964, J. Am. Chem. Soc. 85:2149; Vale et al., 1981, Science 213:1394-1397; Marki et al., 1981, J. Am. Chem. Soc. 103:3178 and in U.S. Patent Nos. 4,305,872 and 4,316,891. In a preferred aspect, an automated peptide synthesizer is employed.

By way of example but not limitation, peptides can be synthesized on an Applied Biosystems Inc. ("ABI") model 431A automated peptide synthesizer using the "Fastmoc" synthesis protocol supplied by ABI, which uses 2-(1H-Benzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate ("HBTU") (R. Knorr et al., 1989, Tet. Lett., 30:1927) as coupling agent. Syntheses can be carried out on 0.25 mmol of commercially available 4-(2',4'-dimethoxyphenyl-(9-fluorenyl-methoxycarbonyl)-aminomethyl)-phenoxy polystyrene resin ("Rink resin" from Advanced ChemTech) (H. Rink, 1987, Tet. Lett. 28:3787). Fmoc amino acids (1 mmol) are coupled according to the Fastmoc protocol. The following side chain protected Fmoc amino acid derivatives are used: FmocArg(Pmc)OH; FmocAsn(Mbh)OH; FmocAsp(^tBu)OH; FmocCys(Acm)OH; FmocGlu(^tBu)OH; FmocGln(Mbh)OH; FmocHis(Tr)OH; FmocLys(Boc)OH; FmocSer(^tBu)OH; FmocThr(^tBu)OH; FmocTyr(^tBu)OH. [Abbreviations: Acm, acetamidomethyl; Boc, tert-butoxycarbonyl; ^tBu, tert-butyl; Fmoc, 9-fluorenylmethoxycarbonyl; Mbh, 4,4'-dimethoxybenzhydryl; Pmc, 2,2,5,7,8-pentamethylchroman-6-sulfonyl; Tr, trityl].

Synthesis is carried out using N-methylpyrrolidone (NMP) as solvent, with HBTU dissolved in N,N-dimethylformamide (DMF). Deprotection of the Fmoc group is effected using approximately 20% piperidine in NMP. At the end of each synthesis the amount of peptide present is assayed by ultraviolet spectroscopy. A sample of dry peptide resin (about 3-10 mg) is weighed, then 20% piperidine in DMA (10 ml) is added. After 30 min sonication, the UV (ultraviolet) absorbance of the dibenzofulvene-piperidine adduct (formed by cleavage of the N-terminal Fmoc group) is

recorded at 301 nm. Peptide substitution (in mmol g⁻¹) can be calculated according to the equation:

$$\text{substitution} = \frac{A \times v}{7800 \times w} \times 1000$$

5 where A is the absorbance at 301 nm, v is the volume of 20% piperidine in DMA (in ml), 7800 is the extinction coefficient (in mol⁻¹dm³cm⁻¹) of the dibenzofulvene-piperidine adduct, and w is the weight of the peptide-resin sample (in mg).

10 Finally, the N-terminal Fmoc group is cleaved using 20% piperidine in DMA, then acetylated using acetic anhydride and pyridine in DMA. The peptide resin is thoroughly washed with DMA, CH₂Cl₂, and finally diethyl ether.

15 6.10.2. Cleavage and Deprotection

By way of example but not limitation, cleavage and deprotection can be carried out as follows: The air-dried peptide resin is treated with ethylmethyl-sulfide (EtSMe), ethanedithiol (EDT), and thioanisole (PhSMe) for
20 approximately 20 min. prior to addition of 95% aqueous trifluoroacetic acid (TFA). A total volume of approximately 50 ml of these reagents are used per gram of peptide-resin. The following ratio is used: TFA:EtSMe:EDT:PhSme (10:0.5:0.5:0.5). The mixture is stirred for 3 h at room
25 temperature under an atmosphere of N₂. The mixture is filtered and the resin washed with TFA (2 x 3 ml). The combined filtrate is evaporated *in vacuo*, and anhydrous diethyl ether added to the yellow/orange residue. The resulting white precipitate is isolated by filtration. See
30 King et al., 1990, Int. J. Peptide Protein Res. 36:255-266 regarding various cleavage methods.

6.10.3. Purification of the Peptides

Purification of the synthesized peptides can be
35 carried out by standard methods including chromatography (e.g., ion exchange, affinity, and sizing column chromatography, high performance liquid chromatography

(HPLC)), centrifugation, differential solubility, or by any other standard technique.

6.10.4. Conjugation of Peptides to Other Molecules

5 The peptides of the present invention may be linked to other molecules (e.g., a detectable label, a molecule facilitating adsorption to a solid substratum, or a toxin, according to various embodiments of the invention) by methods that are well known in the art. Such methods include the use
10 of homobifunctional and heterobifunctional cross-linking molecules.

 The homobifunctional molecules have at least two reactive functional groups, which are the same. The reactive
15 functional groups on a homobifunctional molecule include, for example, aldehyde groups and active ester groups. Homobifunctional molecules having aldehyde groups include, for example, glutaraldehyde and subaraldehyde. The use of glutaraldehyde as a cross-linking agent was disclosed by
20 Poznansky et al., 1984, Science 223:1304-1306.

 Homobifunctional molecules having at least two active ester units include esters of dicarboxylic acids and N-hydroxysuccinimide. Some examples of such N-succinimidyl
25 esters include disuccinimidyl suberate and dithio-bis-(succinimidyl propionate), and their soluble bis-sulfonic acid and bis-sulfonate salts such as their sodium and potassium salts. These homobifunctional reagents are available from Pierce, Rockford, Illinois.

 The heterobifunctional molecules have at least two
30 different reactive groups. Some examples of heterobifunctional reagents containing reactive disulfide bonds include N-succinimidyl 3-(2-pyridyl-dithio)propionate (Carlsson et al., 1978, Biochem J. 173:723-737), sodium S-4-succinimidylloxycarbonyl-alpha-methylbenzylthiosulfate, and
35 4-succinimidylloxycarbonyl-alpha-methyl-(2-pyridyldithio)toluene. N-succinimidyl 3-(2-pyridyldithio)propionate is preferred. Some examples of

heterobifunctional reagents comprising reactive groups having a double bond that reacts with a thiol group include succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate and succinimidyl m-maleimidobenzoate.

5 Other heterobifunctional molecules include succinimidyl 3-(maleimido)propionate, sulfosuccinimidyl 4-(p-maleimido-phenyl)butyrate, sulfosuccinimidyl 4-(N-maleimidomethyl-cyclohexane)-1-carboxylate, maleimidobenzoyl-N-hydroxy-succinimide ester. The sodium sulfonate salt of
10 succinimidyl m-maleimidobenzoate is preferred. Many of the above-mentioned heterobifunctional reagents and their sulfonate salts are available from Pierce.

Additional information regarding how to make and use these as well as other polyfunctional reagents may be
15 obtained from the following publications or others available in the art: Carlsson et al., 1978, Biochem. J. 173:723-737; Cumber et al., 1985, Methods in Enzymology 112:207-224; Jue et al., 1978, Biochem 17:5399-5405; Sun et al., 1974, Biochem. 13:2334-2340; Blattler et al., 1985, Biochem.
20 24:1517-152; Liu et al., 1979, Biochem. 18:690-697; Youle and Neville, 1980, Proc. Natl. Acad. Sci. USA 77:5483-5486; Lerner et al., 1981, Proc. Natl. Acad. Sci. USA 78:3403-3407; Jung and Moroi, 1983, Biochem. Biophys. Acta 761:162; Caulfield et al., 1984, Biochem. 81:7772-7776; Staros, 1982,
25 Biochem. 21:3950-3955; Yoshitake et al., 1979, Eur. J. Biochem. 101:395-399; Yoshitake et al., 1982, J. Biochem. 92:1413-1424; Pilch and Czech, 1979, J. Biol. Chem. 254:3375-3381; Novick et al., 1987, J. Biol. Chem. 262:8483-8487; Lomant and Fairbanks, 1976, J. Mol. Biol. 104:243-261; Hamada
30 and Tsuruo, 1987, Anal. Biochem. 160:483-488; Hashida et al., 1984, J. Applied Biochem. 6:56-63.

Additionally, methods of cross-linking are reviewed by Means and Feeney, 1990, Bioconjugate Chem. 1:2-12.

35 6.10.4.1. Biotinylation of Peptides

Methods of biotinylating peptides are well known in the art. Any convenient method may be employed in the

practice of the invention. For example, the following procedure was used. Ten micrograms of peptide was dissolved in 100 μ l of 0.1 % acetic acid. PBS (900 μ l) and 3.3 mg of biotin-LC-NHS (Pierce, Rockford, IL) was added. Following 5 incubation for 30 minutes at room temperature the biotinylated peptides were purified over a Superose 12 column (Pharmacia, Piscataway, NJ).

6.10.5. Synthetic Peptides

10 Tables 19, 20 and 21 provide the primary structure for various synthetic peptides manufactured in the practice of the present invention.

Table 19		
Seq ID No	Peptide name	Sequence
20	ELAN005	H ₂ N-C-K(dns) - FITKALGISYGRKKRRQRRRPPQGSQTHQVSLSKQ-CONH ₂
	ELAN006	Ac-CLNGGVKMYVESVDRIYVC-CONH ₂
	FITC-ELAN006	Ac-CLNGGVK(FITC)MYVESVDRIYVC-CONH ₂
	ELAN006ii	H ₂ N-C-K(dns) - RLNGGVSMYVESVDRIYVCR-CONH ₂
167	ELAN007	H ₂ N-RIAGLPWYRCRTVAFETGMQNTQLCSTIVQLSFTPEE-COOH
193	ELAN007ii	H ₂ N-KKRIAGLPWYRCRTVAFETGMQNTQLCSTIVQLSFTPEE-CONH ₂
25	bZElan008 (P31)	biotin-K(dns) SARDSGPAEDGSRAVRLNGVENANTRKSSR SNPRGRRHP-COOH
	bZElan009	biotin-K(dns) SSADAEKCAGSLLWWGRQNNSGCGSPTKKH LKHRNRSQTSSSSHG-COOH
	168 ELAN010	H ₂ N-REFAERRLWGCDDLSWRLDAEGCGPTPSNRAVKHRKPRPR SPAL-COOH
30	bZElan010	biotin-K(dns) REFAERRLWGCDDLSWRLDAEGCGPTPSNR AVKHRKPRPRSPAL-COOH
	169 ELAN012	H ₂ N-SGSHSGGMNRAYGDVFRELDRWYATSHHTRPTPQLPRGPN-COOH
	bELAN012	biotin-SGSHSGGMNRAYGDVFRELDRWYATSHHTRPTPQLPRGPN-COOH
35	ZElan012	H ₂ N-K(dns) SGSHSGGMNRAYGDVFRELDRWYATSHHTRPTPQLPRGPN-COOH

5	249	ELAN013	H ₂ N- SGSPPCGGSWGRFMQGGLFGGRTDGCGAHRNRTSASLEPPSSD Y-CONH ₂
	250	ELAN014	H ₂ N- SHSGGMNRAYGDVFRELDRWNATSHHTRPTPQLPRGPNS- CONH ₂
		bZElan014	biotin- K(dns) SHSGGMNRAYGDVFRELDRWNATSHHTRPTPQLPRG PNS-CONH ₂
		ZElan014	H ₂ N- K(dns) SHSGGMNRAYGDVFRELDRWNATSHHTRPTPQLPRG PNS-CONH ₂
		ZElan015 (DCX11)	H ₂ N- K(dns) SQGSKQCMQYRTGRLTVGSEYGCGMNPARGHATPAYPA RLLPRYR-CONH ₂
10		ZElan016 (SNI10)	H ₂ N- K(dns) RVGQCTDSDVRRPWARSCAHQCGAGTRNSHGCITRP LRQASAH-CONH ₂
		bZElan017	biotin-K(dns) SGSGRVGQCTDSDVRRPWARSCA-CONH ₂
		ZElan017	H ₂ N-K(dns) RVGQCTDSDVRRPWARSCA-CONH ₂
		ZElan018 (PAX2)	H ₂ N- K(dns) STPPSREAYSRPYSVSDSDTNAKHSSHNRRLRTRSR PNG-CONH ₂
		ZElan019 (5PAX5)	H ₂ N- K(dns) RGSTGTAGGERSGVNLHTRDNASGSGFKPWYPSNRG HK-CONH ₂
20		ZElan020 (CY09)	H ₂ N-K(dns) SGSGLYANPGMYSRLHSPA-CONH ₂
		bZElan020 (CY09)	biotin-K(dns) SGSGLYANPGMYSRLHSPA-CONH ₂
		ZElan021 (HAX42)	H ₂ N- K(dns) SDHALGTNLRSDNAKEPGDYNCCGNGNSTGRKVFNR RPSAIP-CONH ₂
		ZElan022 (SNI34)	H ₂ N- K(dns) SPCGGSWGRFMQGGLFGGRTDGCGAHRNRTSASLEPP SSDY-CONH ₂
		ZElan023 (DCX8)	H ₂ N- K(dns) RYKHDIGCDAGVDKKSSSVRGCGAHSSPPRAGRGR GTMVSRL-CONH ₂
25		ZElan024 (P31)	H ₂ N- K(dns) SARDSGPAEDGSRAVRLNGVENANTRKSSRSNPRGR HPGG-CONH ₂
		ZElan025 (DAB10)	H ₂ N- K(dns) SKSGEGGDSSRGETGWARVRSHAMTAGRFRWYNQLPS DR-CONH ₂
		ZElan026 (PAX2/control)	H ₂ N- K(dns) SEANLDGRKSRYSPPRNSSTRPRTSPNSVHARYPST DHD-CONH ₂
		bELAN027 (PAX2)	biotin- SGSGSTPPSREAYSRPYSVSDSDTNAKHSSHNRRLRTRSRPN G-CONH ₂
		18C21	H ₂ N-DTNAKHSSHNRRLRTRSRPNG-CONH ₂
35	251	Fmoc- Z16N23	Fmoc-K(dns) RVGQCTDSDVRRPWARSCAHQG-COOH
	252	16C23	H ₂ N-CGAGTRNSHGCITRPLRQASAHG-CONH ₂

	Z16C23	H ₂ N-K (dns) CGAGTRNSHGCITRPLRQASAHG-CONH ₂
	ZElan028	H ₂ N-K (dns) ENANTRKSSRSNPRGRRHPG-CONH ₂
	(P31	
	fragment)	
5	ZElan029	H ₂ N-K (dns) TRKSSRSNPRG-CONH ₂
	(P31	
	fragment)	
	ZElan030	H ₂ N-K (dns) ENANTRKSSRSNPRG-CONH ₂
	(P31	
	fragment)	
	ZElan031	H ₂ N-K (dns) TRKSSRSNPRGRRHPG-CONH ₂
	(P31	
	fragment)	
10	ZElan032	H ₂ N-K (dns) TNAKHSSHNRRLRTRSRPN-CONH ₂
	(PAX2	
	fragment)	
	ZElan033	H ₂ N-K (dns) TNAKHSSHNRRLRTR-CONH ₂
	(PAX2	
	fragment)	
	ZElan034	H ₂ N-K (dns) SSHNRRLRTRSRPN-CONH ₂
	(PAX2	
15	fragment)	
	ZElan035	H ₂ N-K (dns) SSHNRRLRTR-CONH ₂
	(PAX2	
	fragment)	
	ZElan036	H ₂ N-K (dns) VRRPWARSCAHQCGAGTRNS-CONH ₂
	(SNI10	
	fragment)	
20	ZElan037	H ₂ N-K (dns) CTDSVRRPWARSC-CONH ₂
	(SNI10	
	fragment)	
	ZElan038	H ₂ N-
	(PAX2/con	K (dns) SRANTDGRKSRYSPPRRNSSTEPRLSPNSVHARYPST
	trol)	DHD-CONH ₂
	ZElan039	H ₂ N-K (dns) ENANTRKSSR-CONH ₂
	(P31	
25	fragment)	
	ZElan040	H ₂ N-K (dns) SNPRGRRHPG-CONH ₂
	(P31	
	fragment)	
	ZElan041	H ₂ N-K (dns) ENANT-CONH ₂
	(P31	
	fragment)	
30	ZElan042	H ₂ N-K (dns) ANTRKS-CONH ₂
	(P31	
	fragment)	
	ZElan043	H ₂ N-K (dns) TRKSS-CONH ₂
	(P31	
	fragment)	
	ZElan044	H ₂ N-K (dns) RKSSR-CONH ₂
	(P31	
35	fragment)	
	ZElan045	H ₂ N-K (dns) KSSRSN-CONH ₂
	(P31	
	fragment)	

5	ZElan046 (P31 fragment)	H ₂ N-K(dns) SSRSNPG-CONH ₂
	ZElan047 (P31 fragment)	H ₂ N-K(dns) RSNPRG-CONH ₂
	ZElan048 (P31 fragment)	H ₂ N-K(dns) SNPRG-CONH ₂
	ZElan049 (P31 fragment)	H ₂ N-K(dns) PRGRRH-CONH ₂
	ZElan050 (P31 fragment)	H ₂ N-K(dns) RRHPG-CONH ₂
10	ZElan051 (HepC)	H ₂ N-K(dns) KSSRGN-CONH ₂
	ZElan052 (HepC)	H ₂ N-K(dns) KTSERSQPRGRRQPG-CONH ₂
	ZElan053 (P31 analog)	H ₂ N-K(dns) TrKSSrSNPrGrrHPG-CONH ₂
	ZElan054 (P31 analog)	H ₂ N-K(dns) TRKSSrSNPRGrRHPG-CONH ₂
	ZElan055 (PAX2 fragment)	H ₂ N-K(dns) TNAKHSSHN-CONH ₂
20	ZElan056 (PAX2 fragment)	H ₂ N-K(dns) RRLRTRSRPN-CONH ₂
	ZElan057 (PAX2 fragment)	H ₂ N-K(dns) RRLRTRSR-CONH ₂
	ZElan058 (PAX2 fragment)	H ₂ N-K(dns) RRLRTR-CONH ₂
	ZElan059 (PAX2 analog)	H ₂ N-K(dns) rrLrTrSrPN-CONH ₂
	ZElan060 (HAX42 fragment)	H ₂ N-K(dns) SDHALGTNLRSDNAKEPGDYNCCGNG-CONH ₂
30	ZElan061 (HAX42 fragment)	H ₂ N-K(dns) GDYNCCGNGNSTGRKVFNRRRPSAIPT-CONH ₂
	ZElan062 (HAX42 fragment)	H ₂ N-K(dns) SDHALGTNLRSDNAKEPG-CONH ₂
	ZElan063 (HAX42 fragment)	H ₂ N-K(dns) GDYNCCGNGNSTG-CONH ₂
	ZElan064 (HAX42 fragment)	H ₂ N-K(dns) RKVFNRRRPSAIPT-CONH ₂

5	ZElan065 (HAX42 fragment)	H ₂ N-K (dns) RKVFNRRRPS-CONH ₂
	ZElan066 (HAX42 fragment)	H ₂ N-K (dns) NRRRPSAIP-CONH ₂
	ZElan067 (HAX42 fragment)	H ₂ N-K (dns) NRRRPS-CONH ₂
55	Elan018 (PAX2 no dns)	H ₂ N- STPPSREAYSRPYSDSDSDTNAKHSSHNRRRLRTRSRPNG- CONH ₂
10	52 Elan021 (HAX42 no dns)	H ₂ N-SDHALGTNLRSDNAKEPGDYNCCGNGNSTGRKVFNRRRPS AIP-CONH ₂
15	ZElan070 (HAX42 fragment)	H ₂ N-K (dns) SDHALGTNLRSDNAKEPGDYNCCGNGNST- CONH ₂
	ZElan071 (HAX42 fragment)	H ₂ N-K (dns) NLRSDNAKEPGDYNCCGNGNSTGRKVFNR- CONH ₂
	ZElan072 (HAX42 fragment)	H ₂ N-K (dns) PGDYNCCGNGNSTGRKVFNRRPSAIP-CONH ₂
20	ZElan073 (PAX2 fragment)	H ₂ N-K (dns) ASHNRRRLRTR-CONH ₂
	ZElan074 (PAX2 fragment)	H ₂ N-K (dns) SAHNRRRLRTR-CONH ₂
	ZElan075 (PAX2 fragment)	H ₂ N-K (dns) SSANRRRLRTR-CONH ₂
25	ZElan076 (PAX2 fragment)	H ₂ N-K (dns) SSHARRLRTR-CONH ₂
	ZElan077 (PAX2 fragment)	H ₂ N-K (dns) SSHNARLRTR-CONH ₂
	ZElan078 (PAX2 fragment)	H ₂ N-K (dns) SSHNRALRTR-CONH ₂
30	ZElan079 (PAX2 fragment)	H ₂ N-K (dns) SSHNRRARTR-CONH ₂
	ZElan080 (PAX2 fragment)	H ₂ N-K (dns) SSHNRRLATR-CONH ₂
	ZElan081 (PAX2 fragment)	H ₂ N-K (dns) SSHNRRLRAR-CONH ₂
35	ZElan082 (PAX2 fragment)	H ₂ N-K (dns) SSHNRRLRTA-CONH ₂
	Elan035	H ₂ N-SSHNRRRLRTR-CONH ₂

5	ZElan083 (PAX2/control)	H ₂ N-K(dns) GRNHDVVSSNTHKSYRSPRSASYPRLSNDRTDRTEPA PSS-CONH ₂
	ZElan084 (PAX2/control)	H ₂ N-K(dns) RNTRNKTSRLSANPHRSRHR-CONH ₂
	Elan032Z (PAX2 fragment)	H ₂ N-TNAKHSSHNRRRLRTRSRPN K(dns)-CONH ₂
	Elan057Z (PAX2 fragment)	H ₂ N-RRLRTRSRK(dns)-CONH ₂

10

TABLE 20		
Name	Description	Sequence
15	ZElan087	HAX42-1 (20 mer)
	ZElan088	HAX42-2 (20 mer)
	ZElan089	HAX42-3 (15 mer)
	ZElan090	HAX42-4 (15 mer)
	ZElan091	HAX42-5 (14 mer)
	ZElan092	HAX42-6 (10 mer)
	ZElan093	HAX42-7 (10 mer)
20	ZElan100	P31 16 mer cyclic
	ZElan101	P31 16 mer cyclic D form
25	ZElan103	PAX2 15 mer cyclic
	ZElan103A	PAX2 15 mer cyclic (internal)
	ZElan104	PAX2 15 mer cyclic (internal)
35	ZElan105	PAX2 Ala Scan 1
	ZElan106	PAX2 Ala Scan 2
	ZElan107	PAX2 Ala Scan 3
	ZElan108	PAX2 Ala Scan 4
	ZElan109	PAX2 Ala Scan 5
	ZElan110	PAX2 Ala Scan 6
	ZElan111	PAX2 Ala Scan 7
	ZElan112	PAX2 Ala Scan 8

5	ZElan113	PAX2 Ala Scan 9	H ₂ N-K(dns)TNAKHSSSHARRLRTR
	ZElan114	PAX2 Ala Scan 10	H ₂ N-K(dns)TNAKHSSSHNARLRTR
	ZElan115	PAX2 Ala Scan 11	H ₂ N-K(dns)TNAKHSSSHNRALRTR
	ZElan116	PAX2 Ala Scan 12	H ₂ N-K(dns)TNAKHSSSHNRRLRTR
	ZElan117	PAX2 Ala Scan 13	H ₂ N-K(dns)TNAKHSSSHNRRLATR
10	ZElan118	PAX2 Ala Scan 14	H ₂ N-K(dns)TNAKHSSSHNRRLRAR
	ZElan119	PAX2 Ala Scan 15	H ₂ N-K(dns)TNAKHSSSHNRRLRTA
	ZElan123	PAX2 15 mer cyclic D form	H ₂ N-K(dns)Lys-TNAKHSSHNrrLrTr
	ZElan124	PAX2 15 mer D form	H ₂ N-K(dns)TNAKHSSHNrrLrTr
	ZElan125	PAX2 10 mer cyclic	H ₂ N-K(dns)Lys-SSHNRRRLRTR
15	ZElan126	PAX2 10 mer cyclic D form	H ₂ N-K(dns)Lys-SSHNrrLrTr
	ZElan127	PAX2 10 mer cyclic	H ₂ N-K(dns)Lys-TNAKHSSHNr
	ZElan128	PAX2 10 mer cyclic D form	H ₂ N-K(dns)Lys-TNAKHSSHNr
	ZElan129	PAX2 15 mer	H ₂ N-K(dns)TNAKHSSHNRRRLRTR
	ZElan130	HAX42 14 mer Ala Scan 1	H ₂ N-K(dns)AGDYNCCGNGNSTG
20	ZElan131	HAX42 14 mer Ala Scan 2	H ₂ N-K(dns)PADYNCCGNGNSTG
	ZElan132	HAX42 14 mer Ala Scan 3	H ₂ N-K(dns)PGAYNCCGNGNSTG
	ZElan133	HAX42 14 mer Ala Scan 4	H ₂ N-K(dns)PGDANCCGNGNSTG
	ZElan134	HAX42 14 mer Ala Scan 5	H ₂ N-K(dns)PGDYACCGNGNSTG
	ZElan135	HAX42 14 mer Ala Scan 6	H ₂ N-K(dns)PGDYNACGNGNSTG
25	ZElan136	HAX42 14 mer Ala Scan 7	H ₂ N-K(dns)PGDYNACGNGNSTG
	ZElan137	HAX42 14 mer Ala Scan 8	H ₂ N-K(dns)PGDYNCCANGNSTG
	ZElan138	HAX42 14 mer Ala Scan 9	H ₂ N-K(dns)PGDYNCCGAGNSTG
	ZElan139	HAX42 14 mer Ala Scan 10	H ₂ N-K(dns)PGDYNCCGNANSTG
	ZElan140	HAX42 14 mer Ala Scan 11	H ₂ N-K(dns)PGDYNCCGNGASTG
35	ZElan141	HAX42 14 mer Ala Scan 12	H ₂ N-K(dns)PGDYNCCGNGNATG
	ZElan142	HAX42 14 mer Ala Scan 13	H ₂ N-K(dns)PGDYNCCGNGNSAG
	ZElan143	HAX42 14 mer Ala Scan 14	H ₂ N-K(dns)PGDYNCCGNGNSTA

GST fusion proteins of GIT peptides are shown in
Table 21.

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Table 21

Source	Clone #	GST Fusion Sequence	SEQ ID NO.
DCX11	98	gst-SQSKQCMQYRTGRLTVGSEYGCGMNPARHATPAYPARLLPRYR	213
HAX42	99	gst-SDHALGTNLRSDNAKEPGDYNCCGNGNSTGRKVFNRPRPSAIP	214
SNi34	100	gst-SPCGGSGWGRFMQGLFGGRTDGC GAHRNRTSASLEPPSSDY	215
5PAX5	97	gst-RGSTGTAGGERSGVLNLHTRDNASGSGFKPWYPSNRGHK	216
SNi28	84	gst-SHSGGMNRAYGDVVFRELDRDRWNATSHHTRPTPQLPRGPN	217
SNi28	85	gst-SHSGGMNRAY	218
SNi28	86	gst-GDVVFRELDR	219
SNi28	87	gst-WNATSHHTRP	220
SNi28	88	gst-TPQLPRGPN	221
SNi28	89	gst-GDVVFRELDRDRWNATSHHTRP	222
SNi28	90	gst-WNATSHHTRPTPQLPRGPN	223
SNi28	91	gst-GDVVFRELDRDRWNATSHHTRPTPQLPRGPN	224
SNi28	92	gst-SHSGGMNRAYGDVVFRELDRDRWNATSAATRPTPQLPRGPN	225
P31	93	gst-SARDSGPAEDGSAVRLNGVENANTRKSSRSNPRGRHP	226
P31	101	gst-SARDSGPAEDGSAVRLNG	227
P31	102	gst-DGSRAVRLNGVENANTRKSSR	228
P31	103	gst-ENANTRKSSRSNPRGRHP	229
P31	110	gst-ENANTRKSSR	230

P31	111	gst - RKSSRSNPRG	
P31	112	gst - SNPRGRRHP	232
P31	119	gst - TRKSSRSNPRG	233
PAX2	94	gst - STPPSREAYSRPYSDSDTNAKHSSHNRRLLRTRSRPN	234
PAX2	104	gst - STPPSREAYSRPYSDSDSD	235
PAX2	105	gst - SRPYSDSDSDTNAKHSSHN	236
PAX2	106	gst - TNAKHSSHNRRLLRTRSRPN	237
PAX2	113	gst - TNAKHSSHN	238
PAX2	114	gst - SSHNRRLLRTR	239
PAX2	115	gst - RRLRTRSRPN	240
SNi10	96	gst - RVGQCTDSDVRRPWARSCAHQCGAGTRNSHGCI TRPLRQASAH	241
SNi10	116	gst - RVGQCTDSDVRRPWARSCA	242
SNi10	117	gst - VRRPWARSCAHQCGAGTRNS	243
SNi10	118	gst - GTRNSHGCI TRPLRQASAH	244
DCX8	95	gst - RYKHDIGCDAGVDKKSSSVRGCGCAHSSPPRACRGPRGTMVSRL	245
DCX8	107	gst - RYKHDIGCDAGVDKKSSSVRGCGG	246
DCX8	108	gst - GCDAGVDKKSSSVRGCGCAHSSPPRA	247
DCX8	109	gst - GAHSSPPRACRGPRGTMVSRL	248

6.10.6. Peptide Stability

The relative stability for ZElan031, ZElan053 and ZElan054 was determined in simulated intestinal fluid (SIF) SIF was made by dissolving 100mg of pancreatin (Sigma cat#P-5 1625, lot# 122H0812) in 8.4ml of phosphate stock solution, adjusting the pH to 7.5 with 0.2N NaOH and adjusting the volume to 10ml with water.

Peptide (3.25mg) was dissolved in 3.25 ml of 10,000 fold diluted SIF solution at 37°C. Aliquots (0.7ml) of the digestion solution were then withdrawn at <1min, 1h, 3h, and 21h or 24h. The samples were quickly passed through a syringe filter (Millipore Millex-GV 0.22µm, part# SLGV025LS, lot# H2BM95250) and 300µL of the filtered solution was immediately injected onto a Hewlett-Packard HPLC system equipped with a C-8 column (Applied Biosystems column and guard column: column- p/n 0711-0023 Spheri-5 ODS 5µm, 220x4.6mm). The products were eluted at 1.5ml/min using an acetonitrile-water gradient. The major fluorescent peaks were collected, lyophilized and identified by MS analysis.

The HPLC gradient used was:

Time (min)	Solvent Mixture
0	95% H ₂ O-5% acetonitrile (0.1%TFA)
5	95% H ₂ O-5%acetonitrile (0.1%TFA)
35	85% H ₂ O-15% acetonitrile (0.1%TFA) linear solvent change
40	0% H ₂ O-100% acetonitrile (0.1%TFA) "
45	95% H ₂ O-5% acetonitrile (0.1%TFA) "
52	95% H ₂ O-5%acetonitrile (0.1%TFA) "

As shown in Table 22, the relative stability (to SIF) for the three peptides was found to be ZElan053>ZElan054>ZElan031. Enzymatic cleavage of the peptide was found to occur at arginine and/or lysine as expected. The replacement of l-amino acids with their D-amino acid analogs significantly reduced the rate of proteolysis at these residues.

TABLE 22

	<u>Peptide</u>	<u>Percent Remaining at:</u>				<u>Rel. Stab.</u>
		<u>1 m</u>	<u>1 h</u>	<u>3 h</u>	<u>24 h</u>	
5						
	ZElan031	100	38.7	0	0	3
	ZElan054	97.4	58.2	11.6	2.7	2
	ZElan053	100	98.3	98.1	94.0	1

10 7. CHARACTERIZATION OF PEPTIDE-COATED PARTICLES

Binding of Peptide-Coated PLGA Nanoparticles to Fixed Caco-2 Cells

Binding of nanoparticles coated with targeting peptides to fixed Caco-2 cells was investigated using an
 15 ELISA assay based on reaction of antibody with the dansyl moiety present on the peptides. Isoelectric points of selected synthetic peptides are shown in Table 23 (corresponding SEQ ID NOS. are shown in Table 7). Corresponding dansylated synthetic GIT binding peptides are
 20 given in Table 24.

TABLE 23

	<u>Peptide</u>	<u>Sequence</u>	<u>pI</u>
	P31	SARDSGPAEDGSRVRLNGVENANTRKSSRSNPRGRRHP	12.26
25	5PAX5	RGSTGTAGGERSGVLNLHTRDNASGSGFKPWYPSNRGHK	11.49
	SNi10	RVGQCTDSDVRRPWARSCAHQCGAGTRNSHGCITRPLRQASAH	10.45
	SNi34	SPCGGSWGRFMQGGFLGGRTDGCGAHRNRTSASLEPPSSDY	8.25
	DCX11	SQGSKQCMQYRTGRLTVGSEYCGGMNPARHATPAYPARLLPRYR	10.44
	DCX8	RYKHDIGCDAGVDKKSSSVRGCGGAHSSPPRAGRGRGTMVSRL	11.03
	HAX42	SDHALGTNLRSDNAKEPGDYNCCGNGNSTGRKVFNRRRPSAIP	9.62
30	PAX2	STPPSREAYSRPYSVSDSDTNAKHSSHNRRLRTRSRPN	11.26

35

TABLE 24

<u>Peptide</u>	<u>Sequence</u>
P31	H ₂ N-K (dns) SARDSGPAEDGSRVRLNGVENANTRKSSRSNPRGRRHPGG-CONH ₂
5PAX5	H ₂ N-K (dns) RGSTGTAGGERSGVLNLHTRDNASGSGFKPWYPSNRGHK-CONH ₂
5SNI10	H ₂ N-K (dns) RVGQCTDSDVRRPWARS CAHQGCGAGTRNSHGCITRPLRQASAH-CONH ₂
SNI34	H ₂ N-K (dns) SPCGGSWGRFMQGGFLFGGRTDGC GAHRNRTSASLEPPSSDY-CONH ₂
DCX11	H ₂ N-K (dns) SQGSKQCMQYRTGRLTVGSEYGC GMNPARHATPAYPARLLPRYR-CONH ₂
DCX8	H ₂ N-K (dns) RYKHDIGCDAGVDKKSSSVRG GCGAHSSPPRAGRGRGTMTVSRL-CONH ₂
HAX42	H ₂ N-K (dns) SDHALGTNLRS DNAKEPGDYNCCGNGNSTGRKVFNRRRPSA IPT-CONH ₂
PAX2	H ₂ N-K (dns) STPPSREAYSRPYSVDS DSDTNAKHSSHNRRRLRTRSRPNG-CONH ₂
10DAB10	H ₂ N-K (dns) SKSGEGGDSSRGETGWARVR SHAMTAGRFRWYNQLPSDR-CONH ₂

Method:

Confluent Caco-2 monolayers grown in 96-well plates (p38) were fixed and treated with 0.1% phenylhydrazine before blocking with 0.1% BSA in PBS. Control and dansyl peptide-coated nanoparticles were resuspended in sterile water at 10mg/ml and stirred with a magnet for 1h at room temperature. Samples consisted of: (1) blank nanoparticle control, (2) scrambled PAX2-coated nanoparticles, (3) PAX2-coated nanoparticles, (4) HAX42-coated nanoparticles, (5) PAX2/HAX42-coated nanoparticles, and (6) 8 peptide-coated nanoparticles.

Nanoparticles were added to the cells at 10mg/ml in 100μl 1%BSA-PBS (no Tween80 is used in this assay) and 2-fold serially-diluted. The 96-well plates were incubated for 1h at room temperature. The plates were washed 5 times with 1%BSA-PBS and 100μl of anti-dansyl antibody (Cytogen DB3-226.3; 0.5 μg/ml; batch May 1997) was added per well and the plates incubated 1h at room temperature. The wells were washed 5 times with 1%BSA-PBS; 100μl of goat anti-mouse λ:HRP antibody (Southern Biotechnology CN. 1060-05; 1:10,000) was added per well, and the plates incubated 1h at room temperature. After washing 5 times with 1%BSA-PBS, 100μl of TMB peroxidase substrate (KPL CN. 50-76-00) was added to the wells and the optical density at 650nm was measured after 15 minutes.

As shown in Figures 13A-B, a decreasing anti-dansyl ELISA response was observed for nanoparticles coated with PAX2, HAX2, PAX2+HAX2, and a mixture of 8 targeting peptides, when decreasing amounts of the nanoparticles were applied to 5 fixed Caco-2 cells. No concentration effect was observed for blank nanoparticles or nanoparticles coated with a scrambled version of PAX2 peptide. Nanoparticles coated with PAX2, HAX2, PAX2+HAX2, and the 8 peptide mix, showed increased response relative to blank nanoparticles or nanoparticles 10 coated with a scrambled version of PAX2 peptide. The OD values were low relative to those normally observed for GST-peptide fusion binding to fixed Caco-2 cells.

Table 25 below shows the insulin potency and level 15 of peptides coated onto the particles (measured by fluorescence) for formulation 1 particles (formulation by the coacervation method given below).

20

Table 25

	Peptide	Blend	
		Insulin mg/g	Peptide μl/mg
	PAX2	60.7	3.51
	HAX42	55.9	2.93
25	PAX2 SCRAMBLED	57.7	1.26
	P31	67.0	1.22
	5PAX5	52.7	2.83
	SNi10	59.5	1.75
	SNi34	61.5	4.03
	DCX8	59.1	1.87
	DAB10	55.9	1.99

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ELISA of dansylated peptides and insulin coated PLGA particles

The standard ELISA procedure was modified as 35 follows. Peptides and particles were diluted to an appropriate concentration in PBS containing 1%BSA (particles were sonicated to achieve a homogeneous solution), titered

and incubated one hour at room temperature. Following five washes with PBS containing 1%BSA, an in-house IgG1 λ anti-dansyl monoclonal antibody was added (diluted to 1 μ g/ml in 1%BSA-PBS) and the plates were incubated for one hour. After 5 five more washes goat anti-mouse λ -HRP was added (Southern Biotechnology Associates Inc., Birmingham, AL, diluted 1:10,000 in 1%BSA-PBS) and the plates were incubated one hour. After five washes, plates were developed with TMB peroxidase substrate (Kirkegard and Perry, Gaithersburg, MD).

10 All data is presented with background binding subtracted. Tween 20 was not added to the diluent or the washes when insulin coated PLGA particles were included in the assay.

Figures 14A-14B show the binding of the dansylated 15 peptide SNI10 to hSI and BSA.

8. BINDING OF SYNTHETIC PEPTIDES AND PEPTIDE-COATED PARTICLES TO S100 AND P100 FRACTIONS DERIVED FROM CACO-2 CELLS

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8.1. Detection of Binding to Membrane (P100) and Cytosolic (S100) fractions

Caco-2 cell membrane (P100) and cytosolic (S100) fractions were prepared using a modification of the method described in Kinsella, B. T., O'Mahony, D. J. and G. A. 25 FitzGerald, 1994, J. Biol. Chem. 269(47): 29914-29919. Confluent Caco-2 cell monolayers (grown in 75 cm² flasks for up to 1 week at 37°C and 5% CO₂) were washed twice in Dulbecco's PBS (DPBS) and the cells were harvested by 30 centrifugation at 1000 rpm after treatment with 10 mM EDTA-DPBS. The cells were washed 3 times in DPBS and the final cell pellet was resuspended in 3 volumes of ice cold HED buffer (20 mM HEPES (pH 7.67), 1 mM EGTA, 0.5 mM dithiothreitol, 1 mM phenylmethylsulphonyl fluoride (PMSF)). 35 The cells were allowed to swell for 5 min on ice prior to homogenization for 30 sec. The homogenates were centrifuged at 40,000 rpm for 45 min at 4°C. The supernatant (S100) was

removed and the pellet (P100) was resuspended in HEDG buffer (20 mM HEPES (pH 7.67), 1 mM EGTA, 0.5 mM dithiothreitol, 100 mM NaCl, 10% glycerol, 1 mM PMSF). Protein concentrations were determined using the Bradford assay (Bradford, M. M., 5 1976, Anal. Biochem. 72: 248-254).

Binding of peptide and/or peptide-coated PLGA particles to membrane (P100) and cytosolic (S100) fractions was assessed by detection of the dansyl moiety incorporated in the peptide. Costar ninety six well ELISA plates were 10 coated with S100 and P100 fractions (100 µg/ml in 0.05 M NaHCO₃) overnight at 4°C. The plates were blocked with 0.5% bovine serum albumin in DPBS for 1 h at room temperature and washed 3 times in 1% BSA-DPBS. Peptide-coated particles or peptides were dispersed in the same buffer and added to the 15 plates at concentrations in the range 0.0325 - 0.5 mg/well. After 1 h at room temperature the plates were washed 5 times in 1% BSA-DPBS and 100 µl of anti-dansyl antibody (Cytogen DB3-226.3; 0.5 µg/ml) was added per well. The plates were incubated for 1 h at room temperature. The wells were washed 20 3 times in 1% BSA-DPBS and 100 µl of goat anti-mouse IgGλ:HRP antibody (Southern Biotechnology 1060-05; 1:10,000) was added per well. The plates were incubated for 1 h at room temperature. After washing 3 times in 1% BSA-DPBS 100 µl of TMB substrate (3,3',5',5'-tetramethylbenzidine; Microwell 25 Peroxidase Substrate System (Kirkegaard and Perry Laboratories 50-76-00)) was added and the optical density was measured at 650 nm at various time intervals.

8.2. Binding of Peptide-Coated PLGA particles

30 A novel assay system is provided by the instant invention for detection of binding of peptide-coated PLGA particles to membrane (P100) and cytosolic (S100) fractions derived from live Caco-2 cells. The absorbance readings obtained using this assay system were substantially higher 35 than those obtained using similar peptide-coated PLGA particle concentrations on fixed Caco-2 cells. This greater sensitivity together with the derivation of the S100 and P100

fractions from live Caco-2 cells suggests that this assay may be the assay system of choice for detection of peptide-coated PLGA particle binding. The assay was concentration dependent and peptide/particle correlation permitted differentiation
5 between specific and non-specific binding interactions.

Binding of peptide-coated PLGA particles was assessed using S100 and P100 fractions derived from live Caco-2 cells as described above. The fractions were coated onto 96-well plates at 10 μ g/well in 0.05 M NaHCO₃ and peptide-coated PLGA
10 particles were assayed by ELISA at concentrations in the range 0.0325 - 0.5 mg/well.

Figures 15A and 15B illustrate the data obtained on S100 and P100 fractions respectively for particles coated with no peptide, scrambled PAX2 (control), P31 D-Arg 16-mer
15 (ZElan053), HAX42, PAX2 and HAX42/PAX2. Using particle concentrations of 0.0325 - 0.5 mg/well all test peptide-coated PLGA particles exhibited greater binding to both the S100 and P100 fractions than the scrambled PAX2 coated control particles. All particles except P31 D-Arg 16-mer
20 (ZElan053) exhibited greater binding to the P100 fraction than the S100 fraction. Greater binding of the P31 D-Arg 16-mer (ZElan053) coated particles to the S100 fraction may be indicative of non-specific binding due to the D-Arg modification of the P31 peptide (SEQ ID NO:43).

25 Binding of PLGA particles coated with varying concentrations of PAX2 peptide ranging from 0.05 - 5.0 mg/g was assessed using a) fixed Caco-2 cells (P35) and b) S100 and P100 fractions (Caco-2 P33). The particles were assayed at concentrations in the range 0.03125 - 0.0625 mg/well.

30 Using a particle concentration of 0.0625 mg/well, all PAX2 coated particles except those coated at 0.05 mg/g exhibited greater binding to fixed Caco-2 cells than the scrambled PAX2 coated control particles. There appeared to be a concentration effect with increasing PAX2 peptide
35 concentration resulting in improved Caco-2 cell binding (in the range 0.05 - 1.0 mg/g). However all absorbance readings

were low and binding of the PAX2 (5 mg/g) was not consistent with this pattern.

Using particle concentrations of 0.03125 - 0.0625 mg/well all test peptide coated particles except PAX2 (0.05 mg/g) exhibited comparable or greater binding to both the S100 and P100 fractions than the scrambled PAX2 coated control particles. All particles exhibited greater binding to the P100 fraction than the S100 fraction. Binding to both the S100 and P100 fractions was directly proportional to the concentration of the PAX2 peptide on the particle. The absorbance readings obtained using this assay system were substantially higher than those obtained on the fixed Caco-2 cells.

The effect of blocking solution on binding of peptide-coated PLGA particles to P100 fractions (Caco-2 P35) was assessed using 1% bovine serum albumin (BSA) and 1% milk powder blocking solutions to assess background binding. The following particles were assayed at concentrations in the range 0.03125 - 0.0625 mg/well: no peptide; scrambled PAX2; and a range of PAX2 coated particles having peptide concentrations from 5-0.05 mg/g. As previously observed using 1% BSA, all test peptide coated particles except PAX2 coated at 0.05 mg/g exhibited comparable or greater binding to the P100 fractions than the scrambled PAX2 coated control particles. Binding to P100 fractions was directly proportional to the concentration of the PAX2 peptide on the particle (although in this instance PAX2 (5 mg/g) exhibited slightly lower binding than PAX2 (1 mg/g)). A similar trend was observed using 1% milk powder and a particle concentration of 0.0625 mg/well. However all absorbance readings were low when 1% milk powder was used and the binding pattern was not detectable using particles at a concentration of 0.0625 mg/well.

Non-specific binding of peptide-coated PLGA particles to plastic was also assessed using 1% BSA and 1% milk powder blocking solutions. The binding pattern observed above could be detected when BSA was used; however, absorbance readings

were substantially lower and binding of particles PAX2 (0.1 and 0.05 mg/g respectively) was not detectable. When 1% milk powder was used, all absorbance readings were low and no binding pattern was detectable. BSA was chosen for blocking 5 in subsequent assays.

8.3. Comparison of Peptide-Coated Particle and Synthetic Peptide Binding to P100 fractions

Binding of dansylated peptides to P100 fractions 10 was assessed to determine if peptide binding was predictive of peptide-coated particle binding. Figure 16 illustrates the data obtained for the dansylated peptides A) HAX42, P31 D-form and scrambled PAX2 and B) PAX2, HAX42 and scrambled PAX2.

Two consecutive assays produced substantial variations 15 in absorbance readings. Initially, the HAX42 peptide exhibited strong binding when compared to the scrambled PAX2 control. The P31 D-form peptide (ZElan053) exhibited binding at the highest dilution only. In the repeat assay, HAX42 20 also exhibited significant binding compared to the scrambled PAX2 control. However, the scrambled PAX2 control and HAX42 produced relatively high absorbance values compared to those obtained in the previous assay. The PAX2 peptide was indistinguishable from the scrambled PAX2 control.

Peptide/particle binding correlation is summarized as follows 25 in Table 26:

TABLE 26

Peptide/particle assay correlation	
Peptide	Assay correlation
HAX42	+
PAX2	+/-
P31 D-form	-
Scrambled PAX2	+/-
+ positive; +/- equivocal; - negative	

35 Peptide/particle binding correlated well for the HAX42 peptide. In contrast, no correlation could be detected

for the P31 D-form (ZElan053) peptide. Since the P31 D-form peptide-coated particles exhibited greater binding to the S100 fraction than the P100 fraction (unlike the other test peptides) it appears that the particle binding interaction was non-specific or that some other molecule was competing for binding to the P100 fraction but not to the S100 fraction. Thus the peptide/particle assay correlation may be useful for distinguishing between specific and non-specific binding interactions. The scrambled PAX2 control produced variable results so that it was difficult to assess the PAX2 binding correlation.

8.4. Determination of HAX42 and PAX2 Binding Motif Sequences

Peptides and GST fusion proteins of HAX42, PAX2 and various derivatives were assayed using peptide ELISA to P100 membrane fractions derived from Caco-2 cells. The GST-PAX2 protein and PAX2 peptide data indicate that a core binding motif lies in the amino acid sequence TNAKHSSHNRLRTR (SEQ ID NO:) otherwise named GST-106 and ZElan033. Similarly, the HAX42 peptide data suggest that a core binding motif for HAX42 lies in the amino acid sequence PGDYNCCGNCNSTG (SEQ ID NO:), otherwise named ZElan091.

The peptides and proteins were analyzed by a dansylated peptide ELISA method in which 96 well plates were coated overnight at 4°C with 100µl/well coating protein (normally 100µg/ml P100 membrane fraction) in 0.05M carbonate buffer pH9.6. Nonspecific binding was blocked using 200µl/well, 2% Marvel/PBS for 2 hours at 37°C prior to incubation with dansylated peptides. The plates were washed three times with PBS/0.05% Tween 20 and after each subsequent incubation step. The peptides were diluted in blocking solution at a starting concentration of 100µg/ml and diluted 1:2 downwards, 100µl/well, followed by incubation at room temperature for 1 hour, exactly. A buffer blank control was included to ensure that background binding to plastic was not due to the antibodies used in the assay system. To detect the

dansylated peptides, a mouse anti-dansyl antibody (DB3, Cytogen Corp.) at 1:1340 dilution in blocking buffer and 100 μ l/well was added followed by incubation at room temperature for 1 hour. The plates were then incubated with an anti-mouse λ -HRP conjugated antibody (Southern Biotech 1060-05) at a 1:10,000 dilution in blocking solution, 100 μ l/well for 1 hour at room temperature. Plates were developed using 75 μ l/well Bionostics TMB substrate and incubated for approximately 10 minutes. The developing reaction was stopped using Bionostics Red Stop solution (25 μ l/well), and the optical density of the plates was read at 650nm.

GST-PAX2 Peptides - Relative Binding to P100 Fractions

After subtraction of the GST-peptide binding to plastic from P100 binding values, the binding of GST-PAX2 peptides were represented as a ratio of GST-HAX42 binding to P100, which was given the arbitrary value of 1.00. The following ratios were determined from binding to P100 of GST-peptides at a peptide concentration of 20 μ g/ml. Bold denotes positive binding to the P100 membrane fraction.

Table 27

	GST-peptide	Value
25	GST-HAX42	1.00
	GST-PAX2	1.79
	GST-104	0.01
	GST-105	-0.08
	GST-106	2.71
	GST-113	0.26
	GST-114	0.17
	GST-115	0.36
30	GST	0.48

35

Table 28

	GST-peptide Amino Acid Sequence
GST-PAX2	STPPSREAYSRPYSVDSDSDTNAKHSSHNRRLRTRSRPN
GST-104	STPPSREAYSRPYSVDSDSD
GST-105	STPPSREAYSRPYSVDSDSDTNAKHSSHN
5 GST-106	TNAKHSSHNRRLRTRSRPN
GST-113	TNAKHSSHN
GST-114	SSHNRRLRTRSRPN
GST-115	RRLRTRSRPN

- 10 **PAX2 Peptides - Relative Binding to P100 Fractions**
- ZElan021, full length HAX42, was given the arbitrary value of 1.00 for binding to P100 at a given peptide concentration determined from the signal-to-noise ratio data. PAX2 and its derivatives are given as a ratio of HAX42 value to reflect their binding abilities to P100 membrane fractions
- 15 derived from a Caco-2 cell line as shown in Table 29. Table 30 provides a line-up of the PAX2 peptides showing the positive binding peptides in boldface. The GST-PAX2 peptide and PAX2 peptide data agree, demonstrating that a binding motif is in the amino acid sequence TNAKHSSHNRRLRTR (GST-106
- 20 and ZElan033).

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TABLE 29

		Binding value at 20 μ g/ml	Binding value at 20 μ g/ml	Binding value at 50 μ g/ml	Binding value at 50 μ g/ml	Binding value at 50 μ g/ml (Jackson Ab)	Binding value at 50 μ g/ml (Southern Ab)
5	PAX2 peptide						
	ZElan018	-0.33	1.07	0.95	1.01		
	ZElan032	1.43	2.87	0.95	1.06		
	ZElan033	0.35	1.57	0.80	0.66		
	ZElan035	0.12	0.43	0.81	0.77		
	ZElan055	0.99	0.73	1.10	0.59		
	ZElan056	0.00	0.16	0.21	0.21		
	ZElan057	0.08		0.56	0.25		
10	ZElan058	0.05		0.47	0.16		
	ZElan073	0.07		-0.11	0.49	0.66	0.49
	ZElan074	0.06		0.82	0.52	0.71	0.48
	ZElan075	0.13		0.52	0.38	0.47	0.32
	ZElan076	0.08		1.00	0.41	0.60	0.42
	ZElan077	0.20		0.76	0.54	0.73	0.52
	ZElan078	0.11		0.87	0.69	0.68	0.47
	ZElan079	0.31		0.97	0.68	0.83	0.53
	ZElan080	0.23		0.84	0.45	0.67	0.38
15	ZElan081	0.01		0.89	0.47		
	ZElan082	0.00		0.92	0.40		
	ZElan083	0.43	0.63	1.03	0.88		
	ZElan084	1.06	0.93	1.16	0.77		

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Table 30

	PAX2 Peptide	Amino acid sequence	SEQ ID NO:
	ZElan018	H ₂ N-K (dns) STPPSREAYSRPYSVDSDDTNAKHSSHNRRRLRTRSRPNG -CONH ₂	
	ZElan032	H ₂ N-K (dns) TNAKHSSHNRRRLRTRSRPN-CONH ₂	
	ZElan033	H ₂ N-K (dns) TNAKHSSHNRRRLRTR-CONH ₂	
5	ZElan034	H ₂ N-K (dns) SSHNRRRLRTRSRPN-CONH ₂	
	ZElan035	H ₂ N-K (dns) SSHNRRRLRTR-CONH ₂	
	ZElan055	H ₂ N-K (dns) TNAKHSSHN-CONH ₂	
	ZElan056	H ₂ N-K (dns) RRLRTRSRPN-CONH ₂	
	ZElan057	H ₂ N-K (dns) RRLRTRSR-CONH ₂	
	ZElan058	H ₂ N-K (dns) RRLRTR-CONH ₂	
	ZElan059	H ₂ N-K (dns) rrLrTrSrPN-CONH ₂	
	ZElan073	H ₂ N-K (dns) ASHNRRRLRTR-CONH ₂	
	ZElan074	H ₂ N-K (dns) SAHNRRRLRTR-CONH ₂	
10	ZElan075	H ₂ N-K (dns) SSANRRRLRTR-CONH ₂	
	ZElan076	H ₂ N-K (dns) SSHARRLRTR-CONH ₂	
	ZElan077	H ₂ N-K (dns) SSHNARLRTR-CONH ₂	
	ZElan078	H ₂ N-K (dns) SSHNRALRTR-CONH ₂	
	ZElan079	H ₂ N-K (dns) SSHNRRARTR-CONH ₂	
	ZElan080	H ₂ N-K (dns) SSHNRRLATR-CONH ₂	
	ZElan081	H ₂ N-K (dns) SSHNRRRLRAR-CONH ₂	
	ZElan082	H ₂ N-K (dns) SSHNRRRLTA-CONH ₂	
	SCRAMBLED PAX2 PEPTIDES:		
15	ZElan083	H ₂ N-K (dns) GRNHVVSSNTHKSYRSPRSASYPRLSNDRTDRTEPAPSS-CONH ₂	
	ZElan084	H ₂ N-K (dns) RNTRNKTSRLSANPHRSR-CONH ₂	

HAX42 Peptides - Relative Binding to P100 Fractions

ZElan021, full length HAX42, was given the arbitrary
 value of 1.00 for binding to P100 at a given peptide
 20 concentration determined from the signal-to-noise ratio data.
 HAX42 and its derivatives are given as a ratio of HAX42 value
 to reflect their binding abilities to P100 membrane fractions
 derived from a Caco-2 cell line as shown in Table 31. Table
 32 provides a line-up of the HAX42 peptides showing the
 25 positive binding peptides in boldface. A core binding motif
 appears to lie in the amino acid sequence PGDYNCCGNCNSTG
 (ZElan091).

30

35

TABLE 31

HAX42 peptide	Binding value at 20µg/ml	Binding value at 50µg/ml	Binding value at 50µg/ml	Binding value at 25µg/ml	Binding value at 25µg/ml	Binding value at 25µg/ml
ZElan021	1.00	1.00	1.00	1.00	1.00	1.00
ZElan060	0.44	0.56	0.43			
ZElan061	0.20	0.60	0.38			
5 ZElan062	0.11	0.42	0.34			
ZElan065	0.00	0.54	0.30			
ZElan067	0.08	0.52	0.40			
ZElan070	0.59	0.97	0.39			
ZElan071	1.22	0.89	0.75			
ZElan072	0.83	0.61	0.88			
ZElan087				0.46	0.44	
ZElan088				2.21	1.41	1.63
ZElan089				0.55	0.44	0.49
10 ZElan090				2.06	1.54	2.16
ZElan091				2.02	1.37	1.20
ZElan092				1.41	1.90	0.91
ZElan093				1.88	1.37	1.33

Table 32

Amino acid sequence

HAX42 Peptide	Amino acid sequence
15 ZElan021	H ₂ N-K (dns) SDHALGTNLRSDNAKEPGDYNCNGNSTGRKVFNRRRPSAIP-CONH ₂
ZElan060	H ₂ N-K (dns) SDHALGTNLRSDNAKEPGDYNCNG-CONH ₂
ZElan061	H ₂ N-K (dns) GNGNSTGRKVFNRRRPSAIP-CONH ₂
ZElan062	H ₂ N-K (dns) SDHALGTNLRSDNAKEPG-CONH ₂
ZElan065	H ₂ N-K (dns) RKVFNRRRPS-CONH ₂
ZElan067	H ₂ N-K (dns) NRRRPS-CONH ₂
ZElan070	H ₂ N-K (dns) SDHALGTNLRSDNAKEPGDYNCNGNST-CONH ₂
20 ZElan071	H ₂ N-K (dns) NLRSDNAKEPGDYNCNGNSTGRKVFNR-CONH ₂
ZElan072	H ₂ N-K (dns) PGDYNCNGNSTGRKVFNRRRPSAIP-CONH ₂
ZElan087	H ₂ N-K (dns) SDHALGTNLRSDNAKEPGDY-CONH ₂
ZElan088	H ₂ N-K (dns) SDNAKEPGDYNCNGNSTG-CONH ₂
ZElan089	H ₂ N-K (dns) SDHALGTNLRSDNAK-CONH ₂ -CONH ₂
ZElan090	H ₂ N-K (dns) EPGDYNCNGNSTG
ZElan091	H ₂ N-K (dns) PGDYNCNGNSTG-CONH ₂
ZElan092	H ₂ N-K (dns) PGDYNCNG-CONH ₂
25 ZElan093	H ₂ N-K (dns) NCCGNGNSTG-CONH ₂

9. FORMULATIONS

General Method for Preparation of Coacervated Particles.

30 Solid particles containing a Therapeutic as defined herein are prepared using a coacervation method. The are particles are formed from a polymer and have a particle size of between about 10nm and 500 µm, most preferably 50 to 800 nm. In addition the particles contain targeting ligands which are incorporated into the particles using a number of

35 methods.

The organic phase (B) polymer of the general method given above may be soluble, permeable, impermeable,

biodegradable or gastroretentive. The polymer may consist of a mixture of polymer or copolymers and may be a natural or synthetic polymer. Representative biodegradable polymers include without limitation polyglycolides; polylactides; 5 poly(lactide-co-glycolides), including DL, L and D forms; copolyoxalates; polycaprolactone; polyesteramides; polyorthoesters; polyanhydrides; polyalkylcyanoacrylates; polyhydroxybutyrates; polyurethanes; albumin; casein; citosan derivatives; gelatin; acacia; celluloses; polysaccharides; 10 alginic acid; polypeptides; and the like, copolymers thereof, mixtures thereof and stereoisomers thereof. Representative synthetic polymers include alkyl celluloses; hydroxalkyl celluloses; cellulose ethers; cellulose esters; nitrocelluloses; polymers of acrylic and methacrylic acids 15 and esters thereof; dextrans; polyamides; polycarbonates; polyalkylenes; polyalkylene glycols; polyalkylene oxides; polyalkylene terephthalates; polyvinyl alcohols; polyvinyl ethers; polyvinyl esters; polyvinyl halides; polyvinylpyrrolidone; polysiloxanes and polyurethanes and co- 20 polymers thereof.

Typically, particles are formed using the following general method:

An aqueous solution (A) of a polymer, surface active agent, surface stabilising or modifying agent or salt, 25 or surfactant preferably a polyvinyl alcohol (PVA) or derivative with a % hydrolysis 50 - 100% and a molecular weight range 500 - 500,000, most preferably 80-100% hydrolysis and 10,000-150,000 molecular weight, is introduced into a vessel. The mixture (A) is stirred under low shear 30 conditions at 10- 2000 rpm, preferably 100-600 rpm. The pH and/or ionic strength of this solution may be modified using salts, buffers or other modifying agents. The viscosity of this solution may be modified using polymers, salts, or other viscosity enhancing or modifying agents.

35 A polymer, preferably poly(lactide-co-glycolide), polylactide, polyglycolide or a combination thereof or in any enantiomeric form or a covalent conjugate of the these

polymers with a targeting ligand is dissolved in water miscible organic solvents to form organic phase (B). Most preferably, a combination of acetone and ethanol is used in a range of ratios from 0:100 acetone: ethanol to 100: 0

5 acetone: ethanol depending upon the polymer used.

Additional polymer(s), peptide(s) sugars, salts, natural/biological polymers or other agents may also be added to the organic phase (B) to modify the physical and chemical properties of the resultant particle product.

10 A drug or bioactive substance may be introduced into either the aqueous phase (A) or the organic phase (B). A targeting ligand may also be introduced into either the aqueous phase (A) or the organic phase (B) at this point.

The organic phase (B) is added into the stirred
15 aqueous phase (A) at a continuous rate. The solvent is evaporated, preferably by a rise in temperature over ambient and/or the use of a vacuum pump. The particles are now present as a suspension (C). A targeting ligand may be introduced into the stirred suspension at this point.

20 A secondary layer of polymer(s), peptide(s) sugars, salts, natural/biological polymers or other agents may be deposited on to the pre-formed particulate core by any suitable method at this stage.

The particles (D) are then separated from the
25 suspension (C) using standard colloidal separation techniques, preferably by centrifugation at high 'g' force, filtration, gel permeation chromatography, affinity chromatography or charge separation techniques. The supernatant is discarded and the particles (D) re-suspended
30 in a washing solution (E) preferably water, salt solution, buffer or organic solvent(s). The particles (D) are separated from the washing liquid in a similar manner as previously described and re-washed, commonly twice. A targeting ligand may be dissolved in washing solution (E) at the final washing
35 stage and may be used to wash the particles (D).

The particles may then be dried. Particles may then be further processed for example, tabletted, encapsulated or spray dried.

The release profile of the particles formed above 5 may be varied from immediate to controlled or delayed release dependent upon the formulation used and/or desired.

Drug loading may be in the range 0-90% w/w.

Targeting ligand loading may be in the range 0-90% w/w.

Specific examples include the following examples:

10

EXAMPLE 1: Peptide added at the final washing stage

Product: Bovine Insulin loaded nanoparticles

Aim: To prepare a 2g batch of insulin loaded nanoparticles at a theoretical loading of 50mg/g and with the 15 peptide ZElan018 added.

Formulation Details

RG504H	(Lot no. 250583)	2.0g
Acetone		45ml
Ethanol:		5ml
20 PVA (aq. 5%w/v)		400ml
Bovine Insulin (Lot no. 86H0674)		100mg
Peptide: PAX2 (ZElan018)		10mg/50ml dH ₂ O

Experimental details:

25 The 5% w/v PVA solution was prepared by heating water until near boiling point, adding PVA and stirring until cool. The organic phase was prepared by adding acetone, 45ml, and ethanol, 5ml, together. The polymer solution was prepared by adding RG504H, 2g, to the organic phase and 30 stirring until dissolved. The IKA™ reactor vessel was set up, all seals greased and the temperature was set at 25°C. The PVA solution, 400ml, was added into the reactor vessel and stirred at 400 rpm.

Bovine insulin, 100mg, was added into the stirring PVA 35 solution. Using clean tubing and a green needle, the polymer solution was slowly dripped in the stirring PVA solution with the peristaltic pump set at 40. The solvent was allowed to

evaporate by opening the ports and allowing the dispersion to stir overnight at 400 rpm.

The suspension was centrifuged in a Beckman Ultracentrifuge™ with swing-out rotor at 12,500 rpm, 4°C. The 5 supernatant was decanted and discarded. The "cake" of particles was broken up and dH₂O (200mls) was added to wash the particles. The centrifugation and washing steps were repeated twice.

The peptide solution, (ZElan018, 10mg in 50ml dH₂O) 10 was prepared and added to the particles for a final washing stage. The suspended particles were centrifuged as before. The supernatant liquid was decanted, the 'cake' broken up, and the particles were dried in the vacuum oven.

The particles were ground, placed in a securitainer and 15 sent for analysis. The weight of particles recovered was 1.45g. A SEM showed discrete, reasonably spherical particles in the 300-500nm size range. The potency was 49.2mg/g (98.0% of label claim). Peptide loading was 2.42 µg/mg (48.4% of label claim).

20

EXAMPLE 2: Peptide added at the beginning of manufacture

Product: Bovine Insulin loaded nanoparticles

Aim: To prepare a 2g batch of insulin loaded nanoparticles at a theoretical loading of 50mg/g and with the 25 peptide ZElan018 added at the beginning of manufacture.

Formulation Details

RG504H	(Lot no. 250583)	2.0g
Acetone		45ml
Ethanol:		5ml
30 PVA(aq. 5%w/v)		400ml
Bovine Insulin (Lot no. 65H0640)		100mg
Peptide: PAX2 (ZElan018ii)		10mg

Experimental details:

35 The 5% w/v PVA solution was prepared by heating water until near boiling point, adding PVA and stirring until cool. The organic phase was prepared by adding acetone,

45ml, and ethanol, 5ml, together. The polymer solution was prepared by adding RG504H (polyactide-co-glycolide, Boehringer Ingelheim), 2g, to the organic phase prepared in step above and stirring until dissolved. The IKA™ reactor vessel was set up, all seals greased and the temperature was set at 25°C. The PVA solution, 400ml, was added into the reactor vessel and stirred at 400 rpm.

Bovine insulin, 100mg, was added into the stirring PVA solution. PAX2 (ZElan018ii, 10mg) was added to the stirring PVA solution. Using clean tubing and a green needle, the polymer solution was slowly dripped into the stirring PVA solution with the peristaltic pump set at 40. The solvent was allowed to evaporate by opening the ports and allowing the dispersion to stir overnight at 400 rpm. The suspension was centrifuged in a Beckman Ultracentrifuge™ with swing-out rotor at 12,500 rpm, 4°C. The supernatant was decanted and discarded.

The "cake" of particles was broken up and dH₂O (200ml) was added to wash the particles. The centrifugation and washing steps were repeated twice. The 'cake' was broken up and the particles were dried in the vacuum oven.

The particles were ground, placed in a securitainer and sent for analysis. The weight of the particles recovered was 1.6g. The potency was 47.3mg/g (94.6% of label claim). Peptide loading was 1.689µg/mg (33.8% of label claim).

EXAMPLE 3 Peptide added 1 hour before centrifugation

Product: Bovine Insulin loaded nanoparticles

Aim: To prepare a 1g batch of insulin loaded

nanoparticles at a theoretical loading of 50mg/g and with the peptide ZElan018 added 1 hour before centrifugation.

Formulation Details

RG504H	(Lot no. 250583)	1.0g
Acetone		22.5ml
Ethanol:		2.5ml
PVA(aq. 5%w/v)		200ml
Bovine Insulin	(Lot no. 65H0640)	50mg

Peptide: PAX2 (ZElan018)

5mg

Experimental details:

The 5% w/v PVA solution was prepared by heating 5 water until near boiling point, adding PVA and stirring until cool. The organic phase was prepared by adding acetone, 22.5ml, and ethanol, 2.5ml, together. The polymer solution was prepared by adding RG504H, 1g, to the organic phase prepared above and stirring until dissolved. The IKA™ 10 reactor vessel was set up, all seals greased and the temperature was set at 25°C. The PVA solution, 200ml, was added into the reactor vessel and stirred at 400 rpm.

Bovine insulin, 50mg, was added into the stirring PVA solution. Using clean tubing and a green needle, the 15 polymer solution was slowly dripped in the stirring PVA solution with the peristaltic pump set at 40. The solvent was allowed to evaporate by opening the ports and allowing the dispersion to stir overnight at 400 rpm.

PAX2 (ZElan018 5mg) was added to the stirring 20 particle suspension. After 1 hr, the suspension was centrifuged in a Beckman Ultracentrifuge™ with swing-out rotor at 12,500 rpm, 4°C. The supernatant was decanted and discarded. The "cake" of particles was broken up and dH₂O (200ml) was added to wash the particles. The centrifugation 25 and washing steps were repeated twice.

The 'cake' was broken up and the particles were dried in the vacuum oven. The particles were ground, placed in a securitainer and sent for analysis. Potency was 20.75mg/g (41.5% of label claim). Peptide loading was 30 1.256µg/mg (25.12 % of label claim).

EXAMPLE 4: Leuprolide acetate loaded nanoparticles

Aim: To prepare a 3g batch of leuprolide-acetate loaded nanoparticles at a theoretical loading of 20mg/g and with the 35 peptide ZElan024 added.

Formulation Details

RG504H (Lot no. 271077)

3.0g

Acetone	67.5ml
Ethanol:	7.5ml
PVA(aq. 5%w/v)	600ml
Leuprolide acetate (Lot no. V14094)	60mg
5 Peptide: P31 (ZElan024)	15mg/50ml dH ₂ O

Experimental details:

The PVA solution was prepared and the organic phase was prepared by adding acetone, 67.5ml, and ethanol, 7.5ml, together. The polymer solution was prepared by adding RG504H, 3g, to the organic phase prepared above and stirring until dissolved. The IKA™ reactor vessel was set up, all seals greased and the temperature was set at 25°C. The PVA solution, 600ml, was added into the reactor vessel and stirred at 400 rpm.

Leuprolide acetate, 60mg, was added into the stirring PVA solution. Using clean tubing and a green needle, the polymer solution, was slowly dripped in the stirring PVA solution with the peristaltic pump set at 40. The solvent was allowed to evaporate by opening the ports and allowing the dispersion to stir overnight at 400 rpm. The suspension was centrifuged in a Beckman Ultracentrifuge™ with swing-out rotor at 15,000 rpm, 4°C. The supernatant was decanted and retained for analysis.

The "cake" of particles was broken up and dH₂O (200ml) was added to wash the particles. The centrifugation and washing steps were repeated twice.

The peptide solution (P31 (SEQ ID NO:43), 15mg in 50ml dH₂O) was prepared and added to the particles for a final washing stage. The suspended particles were centrifuged as before. The supernatant liquid was decanted, and the particles were dried in the vacuum oven.

The particles were ground, placed in a securitainer and sent for analysis. The weight of particles recovered was 1.87g. SEM showed discrete, reasonably spherical particles in the 300-500nm size range. The potency was 4.7mg/g (23.4% of label claim). Peptide loading was 1.76µg/mg.

EXAMPLE 5: Peptide added by 'spiking' polymer phase with polymer-peptide conjugate

Product: Bovine Insulin loaded nanoparticles

Aim: To prepare a 3g batch of insulin loaded
5 nanoparticles at a theoretical loading of 50mg/g and with the polymer-peptide conjugate PLGA-ZElan019 added.

Formulation Details

RG504H	(Lot no. 271077)	2.85g
RG504H-ZElan019 conjugate		0.15g
10	(5PAX5-conjugate)	
Acetone		67.5ml
Ethanol:		7.5ml
PVA(aq. 5%w/v)		600ml
Bovine Insulin(Lot no. 86H0674)		150mg

15

Experimental details:

The 5% w/v PVA solution was prepared by heating water until near boiling point, adding PVA and stirring until cool. The organic phase was prepared by adding acetone,
20 67.5ml, and ethanol, 7.5ml, together. The polymer solution was prepared by adding RG504H and the polymer-peptide conjugate to the organic phase and stirring until dissolved.

The IKA™ reactor vessel was set up, all seals greased and the temperature was set at 25°C. The PVA
25 solution, 400ml, was added into the reactor vessel and stirred at 400 rpm.

Bovine insulin, 100mg, was added into the stirring PVA solution. Using clean tubing and a green needle, the polymer solution, was slowly dripped in the stirring PVA
30 solution with the peristaltic pump set at 40. The solvent was allowed to evaporate by opening the ports and allowing the dispersion to stir overnight at 400 rpm.

The suspension was centrifuged in a Beckman Ultracentrifuge™ with swing-out rotor at 12,500 rpm, 4°C.
35 The supernatant was decanted and discarded. The "cake" of particles was broken up and dH₂O (200ml) was added to wash the

particles. The centrifugation washing step was repeated twice.

The 'cake' was broken up and the particles were dried in the vacuum oven. The particles were ground, placed in a securitainer and sent for analysis. The weight of particles recovered was 2.8g. The potency was 53.1mg/g (106.2% of label claim). Peptide loading was 4.02 μ g/mg (80.4% of label claim).

10 10. ANIMAL STUDIES

Study 1

An open-loop study in which the test solution was injected directly into the ileum was done. Wistar rats (300-350g) were fasted for 4 hours and anaesthetized by intramuscular administration 15 to 20 minutes prior to administration of the test solution with a solution of ketamine [0.525 ml of ketamine (100 mg/ml) and 0.875 ml of acepromazine maleate-BP ACP (2mg/ml)]. The rats were then injected with a test solution (injection volume: 1.5ml PBS) intra-duodenally at 2-3 cm below the pylorus. The test solution contained either PLGA particles manufactured according to the coacervation procedure given above with or without targeting peptides or by the "spiked" method given above. Insulin (fast-acting bovine; 28.1 iu/mg) was incorporated in the particles at 5% drug loading for a total of 100iu insulin (70 mg particles) or 300iu insulin (210 mg particles). Blood glucose values for the rats were measured using a Glucometer™ (Bayer; 0.1 to 33.3 m/mol/L); plasma insulin values were measured using a Phadeseph RIA Kit™ (Upjohn Pharmacia; 3 to 240 μ U/ml-assayed in duplicate). Systemic and portal blood was sampled.

Study groups included animals receiving test solutions containing particles coated with the following peptides shown in Table 33.

Table 33

	Study Group	Receptor	Peptide
	I	hSI	SNi10
			SNi34
5	II	hPEPT1	P31
			5PAX5
	III	HPT1	PAX2
			HAX42
	IV	D2H	DCX8
			DCX11
10	V ("spiked")	hPEPT1	P31-PLGA conjugate
			5PAX5-PLGA conjugate

Control groups included: 1) PBS control (1.5ml) Open-Loop;
 15 2) Insulin solution (1iu/0.2ml) subcutaneous; 3) Insulin particles - no peptide (1iu/0.2ml) subcutaneous; 4) Insulin particles/all 8 peptides mix (1iu/0.2ml) subcutaneous; 5) Insulin loaded particles/peptide control (scrambled 5PAX5) (100iu/1.5ml) Open-Loop; 6) Insulin loaded particles/peptide control (scrambled 5PAX5) (300iu/1.5ml) Open-Loop; 7) Control
 20 particles (insulin-free)/all 8 peptide mix (equivalent 100iu/1.5ml) Open-Loop; and 8) Control particles (insulin-free)/all 8 peptide mix (equivalent 300iu/1.5ml) Open-Loop.

The following describes the pharmacokinetics for
 25 300iu-loading:

	Target Receptor	F%*	Fold-increase**	Stat. Sig.**
	HPT1	10.37	17.0	<0.001
	Spiked hPEPT1	4.94	7.5	0.005
	PAX2 scrambled	3.50	3.6	NS
	Mix-8	2.00	2.0	NS
	hPEPT1	1.60	1.5	NS
30	D2H	1.57	1.4	NS
	hSI	0.54	0.9	NS

* based on area under the curve (AUC) (1-4h), base-line adjusted, relative to subcutaneous insulin solution 1iu
 ** Fold increase in AUC compared to insulin particles: 300iu

35 Figures 17A and 17B show the systemic blood glucose and insulin levels following intestinal administration of control (PBS); insulin solution; insulin particles; all 8

peptides mix particles and study group peptide-particles (100iu). Figures 18A and 18B show the systemic blood glucose and insulin levels following intestinal administration of control (PBS); insulin solution; insulin particles and study 5 group peptide-particles (300iu).

HPT1 targeted peptide coated particles provided the most potent enhancement of the delivery of insulin over subcutaneous injection of insulin followed by hPEPT1 spiked > PAX2 scrambled > mix-8 > hPEPT1 > D2H > uncoated particles > 10 hSI > solution. In a repeat study, the uncoated particles containing insulin gave similar profiles but the HPT1-peptide targeted particles gave a reduced profile (3-fold). The insulin-free PLGA particles and the all-8 mix particles did not show an effect on the basal insulin or glucose levels.

15 The HPT1 targeting particles, the PEPT1 spiked, targeting particles, and the PEPT1 targeting particles also reduced blood glucose levels indicative that the insulin delivered was bioactive. The other targeting particles were also shown to reduce blood glucose levels although not to the same 20 extent as the HPT1 and PEPT1 spiked particles. No histological differences were observed in the small intestine for any of the formulations evaluated.

Study 2

25 A second open-loop study, similar to study 1 above, was undertaken with the following treatment groups as shown in Table 34.

Table 34

30

	Group Number	Dose Insulin (iu)	Description
	1		PBS control
35	2a	1	subcutaneous, bovine insulin
	2b	2	subcutaneous, bovine insulin
	2c	3	subcutaneous, bovine insulin
	2d	4	subcutaneous, bovine insulin
	2e	10	subcutaneous, bovine insulin

	2f	20	subcutaneous, bovine insulin
	2g	4	subcutaneous, human insulin
	3	300	uncoated insulin particles
	4	100	HAX42/PAX2 with 300 iu particle loading
5	5	300	HAX42/PAX2 (40mer) particles
	6	300	HAX42 (40mer) particles
	7	300	HAX42 particles + 10-fold excess free HAX42 (40mer)
	8	300	PAX2 (40mer) particles
	9	300	PAX2 freeze-dried (40mer) particles
	10	300	PAX2 scrambled particles III (40mer)
10	11	300	PAX2 scrambled particles IV (19mer)
	12	300	5PAX5/P31 (40mer) particles
	13	300	P31 (40mer) particles
	14	300	5PAX5 (40mer) particles
	15	300	HAX42 (27mer) particles
15	16	300	PAX2 (20mer) particles
	17	300	P31 (20mer) particles
	18	300	PAX2 (15mer) particles
	19	300	P31 (15mer) particles
	20	300	P31 D-form I(5 D-arginine) (16mer) particles
20	21	300	P31 D-form II(2 D-arginine) (16mer) particles
	22	300	HAX42 (10mer)

Availability of insulin following administration was assessed relative to a 1 and 20iu subcutaneous dose because the response to increasing subcutaneous doses of bovine insulin does not increase linearly over the range of 1 to 20iu. Data up to three hours post-dosing was available for most animals. Therefore, availability was first assessed using individual AUC(0-3h) data estimated from baseline-subtracted data for which data up to 3 hours was available. This approach may lead to an underestimation of the availability as some animals that gave a high response often did not survive for 3 hours and, therefore, were excluded from the analyses. In an attempt to capture as much of these high responses observed at the earlier timepoints as possible, the mean baseline-subtracted plasma concentration

data was used to estimate an AUC for each group. Table 35 shows the results based on this second approach (AUC(0-3h) calculated from the mean plasma concentration data).

5

Table 35

Group	Dose iu	Mean AUC _(0-3h)	F vs. 1 iu	F vs. 20 iu
1	0	2.14		
2a	1	875.27	100.00	28.86
2b	2	2439.36	139.35	40.22
2c	3	3671.44	139.82	40.36
2d	4	6912.18	197.43	56.98
2e	10	27224.41	311.04	89.77
2f	20	60651.28	346.47	100.00
2g	4	14255.49	407.17	117.52
3	300	10677.78	4.07	1.17
3 -Rat43	300	4645.06	1.77	0.51
4	100	3527.18	4.03	1.16
5	300	27112.26	10.33	2.98
6	300	33091.68	12.60	3.64
7	300	9303.09	3.54	1.02
8	300	34241.83	13.04	3.76
9	300	10968.83	4.18	1.21
10	300	27692.78	10.55	3.04
11	300	3004.29	1.14	0.33
12	300	18852.61	7.18	2.07
13	300	20278.43	7.72	2.23
14	300	17400.38	6.63	1.91
15	300	16775.69	6.39	1.84
16	300	14217.47	5.41	1.56
17	300	8197.97	3.12	0.90
18	300	25050.59	9.54	2.75
19	300	7927.96	3.02	0.87
20	300	21519.57	8.20	2.37
21	300	6322.41	2.41	0.69
22	300	12553.01	4.78	1.38

The data for group 3 (uncoated insulin particles) are expressed with and without Rat 43. This animal had an atypically high response to these uncoated particles and, therefore, may have biased the data for this group.

This data shows that a combination of peptide-coated particles (HAX42/PAX2 or 5PAX5/P31) shows no greater availability than particles coated with the individual peptides. Further, peptide-coated particles have a greater availability than uncoated peptides. Scrambling the 40mer

PAX2 peptide did not result in a loss of bioavailability. Scrambling the PAX2 peptide and reducing the size to 19mer resulted in a loss of bioavailability although this loss may be attributed in part to the reduction in peptide size.

5 Reducing peptide size resulted in loss of bioavailability. The D-form of P31 (ZElan053) had increased bioavailability possibly due to greater resistance to peptide breakdown. A competitive excess of peptide resulted in a loss of bioavailability, and freeze drying caused a loss in
10 bioavailability. By way of example, measurement of blood glucose levels showed that the HPT1 and hPEPT1 targeting particles incorporating HAX42, PAX2, P31 (SEQ ID NO:43), and P31 D-form (ZElan053) reduced blood glucose levels indicating that the insulin delivered was bioactive.

15 In further studies, insulin was recovered from the targeting particles following particle formation by dissolution and analyzed by electrophoresis in non-denaturing sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis (PAGE). The analysis of the insulin by non-
20 denaturing SDS-PAGE and also by western blot transferred to membranes and subsequent screening with an antibody to insulin, indicated that the insulin was intact, with no evidence of degradation, dimerization, or aggregation during the process of particle formation.

25

Study 3

An intraduodenal open loop model study was carried out on Wistar rats (300-350g). Group 1 was administered leuprolide acetate (12.5 μ g) subcutaneously. Group 2 was
30 administered intraduodenally uncoated leuprolide acetate particles (600 μ g, 1.5 ml). Group 3 was intraduodenally administered leuprolide acetate particles coated with PAX2 (600 μ g; 1.5 ml). Group 4 was administered intraduodenally leuprolide acetate particles coated with P31 (SEQ ID NO:43)
35 (600 μ g, 1.5 ml). Figure 19 shows the leuprolide plasma concentration following administration to these four groups. Both the P31 (SEQ ID NO:43) and the PAX2 coated leuprolide

particles administered intraduodenally provided enhanced plasma levels of leuprolide relative to subcutaneous injection.

- 5 Homologies of GIT transport-binding peptides to known proteins are shown in Figures 20, 21A-F, and 22 A-D.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed,
10 various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

- 15 Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

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SEQUENCE LISTING

(1) GENERAL INFORMATION

- 5 (i) APPLICANTS: CYTOGEN CORPORATION and ÉLAN CORPORATION, plc
- (ii) TITLE OF THE INVENTION: RANDOM PEPTIDES THAT BIND TO GASTRO-INTESTINAL TRACT (GIT) TRANSPORT RECEPTORS AND RELATED METHODS
- (iii) NUMBER OF SEQUENCES: 265
- (iv) CORRESPONDENCE ADDRESS:
- 10 (A) ADDRESSEE: Pennie & Edmonds LLP
(B) STREET: 1155 Avenue of the Americas
(C) CITY: New York
(D) STATE: New York
(E) COUNTRY: USA
(F) ZIP: 10036
- (v) COMPUTER READABLE FORM:
- 15 (A) MEDIUM TYPE: Diskette
(B) COMPUTER: IBM Compatible
(C) OPERATING SYSTEM: DOS
(D) SOFTWARE: FastSEQ Version 2.0
- (vi) CURRENT APPLICATION DATA:
- (A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:
- (viii) ATTORNEY/AGENT INFORMATION:
- 20 (A) NAME: Misrock, S. Leslie
(B) REGISTRATION NUMBER: 18,872
(C) REFERENCE/DOCKET NUMBER: 1101-209-228
- (ix) TELECOMMUNICATION INFORMATION:
- (A) TELEPHONE: 212-790-9090
(B) TELEFAX: 212-869-9741
(C) TELEX: 66141 PENNIE

25

(2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown
- 30 (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:
- | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Ser | Gly | Ala | Tyr | Glu | Ser | Pro | Asp | Gly | Arg | Gly | Gly | Arg | Ser | Tyr |
| 1 | | | | 5 | | | | | 10 | | | | 15 | | |
| Val | Gly | Gly | Gly | Gly | Gly | Cys | Gly | Asn | Ile | Gly | Arg | Lys | His | Asn | Leu |
| | | 20 | | | | | | 25 | | | | | 30 | | |
| Trp | Gly | Leu | Arg | Thr | Ala | Ser | Pro | Ala | Cys | Trp | Asp | | | | |
| | | 35 | | | | | 40 | | | | | | | | |
- 35

(2) INFORMATION FOR SEQ ID NO:2:

- (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```

Ser Pro Arg Ser Phe Trp Pro Val Val Ser Arg His Glu Ser Phe Gly
 1           5           10           15
Ile Ser Asn Tyr Leu Gly Cys Gly Tyr Arg Thr Cys Ile Ser Gly Thr
          20           25           30
Met Thr Lys Ser Ser Pro Ile Tyr Pro Arg His Ser
      35           40

```

10 (2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```

Ser Ser Ser Ser Asp Trp Gly Gly Val Pro Gly Lys Val Val Arg Glu
 1           5           10           15
Arg Phe Lys Gly Arg Gly Cys Gly Ile Ser Ile Thr Ser Val Leu Thr
          20           25           30
Gly Lys Pro Asn Pro Cys Pro Glu Pro Lys Ala Ala
      35           40

```

20 (2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```

Arg Val Gly Gln Cys Thr Asp Ser Asp Val Arg Arg Pro Trp Ala Arg
 1           5           10           15
Ser Cys Ala His Gln Gly Cys Gly Ala Gly Thr Arg Asn Ser His Gly
          20           25           30
Cys Ile Thr Arg Pro Leu Arg Gln Ala Ser Ala His
      35           40

```

30 (2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

35 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Ser His Ser Gly Gly Met Asn Arg Ala Tyr Gly Asp Val Phe Arg Glu
 1 5 10 15
 Leu Arg Asp Arg Trp Asn Ala Thr Ser His His Thr Arg Pro Thr Pro
 20 25 30
 Gln Leu Pro Arg Gly Pro Asn
 35

5 (2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 41 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Ser Pro Cys Gly Gly Ser Trp Gly Arg Phe Met Gln Gly Gly Leu Phe
 1 5 10 15
 Gly Gly Arg Thr Asp Gly Cys Gly Ala His Arg Asn Arg Thr Ser Ala
 20 25 30
 Ser Leu Glu Pro Pro Ser Ser Asp Tyr
 35 40

15

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Arg Gly Ala Ala Asp Gln Arg Arg Gly Trp Ser Glu Asn Leu Gly Leu
 1 5 10 15
 Pro Arg Val Gly Trp Asp Ala Ile Ala His Asn Ser Tyr Thr Phe Thr
 20 25 30
 Ser Arg Arg Pro Arg Pro Pro
 35

25

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Ser Gly Gly Glu Val Ser Ser Trp Gly Arg Val Asn Asp Leu Cys Ala
 1 5 10 15
 Arg Val Ser Trp Thr Gly Cys Gly Thr Ala Arg Ser Ala Arg Thr Asp
 20 25 30
 Asn Lys Gly Phe Leu Pro Lys His Ser Ser Leu Arg
 35 40

35

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```

Ser Asp Ser Asp Gly Asp His Tyr Gly Leu Arg Gly Gly Val Arg Cys
 1          5          10          15
Ser Leu Arg Asp Arg Gly Cys Gly Leu Ala Leu Ser Thr Val His Ala
          20          25          30
Gly Pro Pro Ser Phe Tyr Pro Lys Leu Ser Ser Pro
          35          40

```

10

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

15

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```

Arg Ser Leu Gly Asn Tyr Gly Val Thr Gly Thr Val Asp Val Thr Val
 1          5          10          15
Leu Pro Met Pro Gly His Ala Asn His Leu Gly Val Ser Ser Ala Ser
          20          25          30
Ser Ser Asp Pro Pro Arg Arg
          35

```

20

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

25

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```

Arg Thr Thr Thr Ala Lys Gly Cys Leu Leu Gly Ser Phe Gly Val Leu
 1          5          10          15
Ser Gly Cys Ser Phe Thr Pro Thr Ser Pro Pro Pro His Leu Gly Tyr
          20          25          30
Pro Pro His Ser Val Asn
          35

```

30

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

35

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Ser Pro Lys Leu Ser Ser Val Gly Val Met Thr Lys Val Thr Glu Leu
 1 5 10 15
 Pro Thr Glu Gly Pro Asn Ala Ile Ser Ile Pro Ile Ser Ala Thr Leu
 20 25 30
 Gly Pro Arg Asn Pro Leu Arg
 35

5 (2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Arg Trp Cys Gly Ala Glu Leu Cys Asn Ser Val Thr Lys Lys Phe Arg
 1 5 10 15
 Pro Gly Trp Arg Asp His Ala Asn Pro Ser Thr His His Arg Thr Pro
 20 25 30
 Pro Pro Ser Gln Ser Ser Pro
 35

15

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Arg Trp Cys Gly Ala Asp Asp Pro Cys Gly Ala Ser Arg Trp Arg Gly
 1 5 10 15
 Gly Asn Ser Leu Phe Gly Cys Gly Leu Arg Cys Ser Ala Ala Gln Ser
 20 25 30
 Thr Pro Ser Gly Arg Ile His Ser Thr Ser Thr Ser
 35 40

25

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Ser Lys Ser Gly Glu Gly Gly Asp Ser Ser Arg Gly Glu Thr Gly Trp
 1 5 10 15
 Ala Arg Val Arg Ser His Ala Met Thr Ala Gly Arg Phe Arg Trp Tyr
 20 25 30
 Asn Gln Leu Pro Ser Asp Arg
 35

35

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```

Arg Ser Ser Ala Asn Asn Cys Glu Trp Lys Ser Asp Trp Met Arg Arg
 1           5           10           15
Ala Cys Ile Ala Arg Tyr Ala Asn Ser Ser Gly Pro Ala Arg Ala Val
          20           25           30
Asp Thr Lys Ala Ala Pro
          35

```

10

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```

Ser Lys Trp Ser Trp Ser Ser Arg Trp Gly Ser Pro Gln Asp Lys Val
 1           5           10           15
Glu Lys Thr Arg Ala Gly Cys Gly Gly Ser Pro Ser Ser Thr Asn Cys
          20           25           30
His Pro Tyr Thr Phe Ala Pro Pro Pro Gln Ala Gly
          35           40

```

20

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```

Ser Gly Phe Trp Glu Phe Ser Arg Gly Leu Trp Asp Gly Glu Asn Arg
 1           5           10           15
Lys Ser Val Arg Ser Gly Cys Gly Phe Arg Gly Ser Ser Ala Gln Gly
          20           25           30
30 Pro Cys Pro Val Thr Pro Ala Thr Ile Asp Lys His
          35           40

```

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```

Ser Glu Ser Gly Arg Cys Arg Ser Val Ser Arg Trp Met Thr Thr Trp
 1           5           10
Gln Thr Gln Lys Gly Gly Cys Gly Ser Asn Val Ser Arg Gly Ser Pro
      20           25           30
Leu Asp Pro Ser His Gln Thr Gly His Ala Thr Thr
      35           40

```

5 (2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 39 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```

Arg Glu Trp Arg Phe Ala Gly Pro Pro Leu Asp Leu Trp Ala Gly Pro
 1           5           10
Ser Leu Pro Ser Phe Asn Ala Ser Ser His Pro Arg Ala Leu Arg Thr
      20           25           30
Tyr Trp Ser Gln Arg Pro Arg
      35

```

15

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 44 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```

Arg Met Glu Asp Ile Lys Asn Ser Gly Trp Arg Asp Ser Cys Arg Trp
 1           5           10
Gly Asp Leu Arg Pro Gly Cys Gly Ser Arg Gln Trp Tyr Pro Ser Asn
      20           25           30
Met Arg Ser Ser Arg Asp Tyr Pro Ala Gly Gly His
      35           40

```

25

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 36 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: unknown

30

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```

Ser His Pro Trp Tyr Arg His Trp Asn His Gly Asp Phe Ser Gly Ser
 1           5           10
Gly Gln Ser Arg His Thr Pro Pro Glu Ser Pro His Pro Gly Arg Pro
      20           25           30
35 Asn Ala Thr Ile
      35

```

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```

Arg Tyr Lys His Asp Ile Gly Cys Asp Ala Gly Val Asp Lys Lys Ser
 1           5           10           15
Ser Ser Val Arg Gly Gly Cys Gly Ala His Ser Ser Pro Pro Arg Ala
          20           25           30
Gly Arg Gly Pro Arg Gly Thr Met Val Ser Arg Leu
      35           40

```

10

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```

Ser Gln Gly Ser Lys Gln Cys Met Gln Tyr Arg Thr Gly Arg Leu Thr
 1           5           10           15
Val Gly Ser Glu Tyr Gly Cys Gly Met Asn Pro Ala Arg His Ala Thr
          20           25           30
Pro Ala Tyr Pro Ala Arg Leu Leu Pro Arg Tyr Arg
      35           40

```

20

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```

Ser Gly Arg Thr Thr Ser Glu Ile Ser Gly Leu Trp Gly Trp Gly Asp
 1           5           10           15
Asp Arg Ser Gly Tyr Gly Trp Gly Asn Thr Leu Arg Pro Asn Tyr Ile
          20           25           30
Pro Tyr Arg Gln Ala Thr Asn Arg His Arg Tyr Thr
      35           40

```

30

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Arg Trp Asn Trp Thr Val Leu Pro Ala Thr Gly Gly His Tyr Trp Thr
 1 5 10 15
 Arg Ser Thr Asp Tyr His Ala Ile Asn Asn His Arg Pro Ser Ile Pro
 20 25 30
 His Gln His Pro Thr Pro Ile
 35

5 (2) INFORMATION FOR SEQ ID NO:27:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 44 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Ser Trp Ser Ser Trp Asn Trp Ser Ser Lys Thr Thr Arg Leu Gly Asp
 1 5 10 15
 Arg Ala Thr Arg Glu Gly Cys Gly Pro Ser Gln Ser Asp Gly Cys Pro
 20 25 30
 Tyr Asn Gly Arg Leu Thr Thr Val Lys Pro Arg Thr
 35 40

15

(2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 37 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

20

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Ser Gly Ser Leu Asn Ala Trp Gln Pro Arg Ser Trp Val Gly Gly Ala
 1 5 10 15
 Phe Arg Ser His Ala Asn Asn Asn Leu Asn Pro Lys Pro Thr Met Val
 20 25 30
 Thr Arg His Pro Thr
 35

25

(2) INFORMATION FOR SEQ ID NO:29:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 44 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

30

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Arg Tyr Ser Gly Leu Ser Pro Arg Asp Asn Gly Pro Ala Cys Ser Gln
 1 5 10 15
 Glu Ala Thr Leu Glu Gly Cys Gly Ala Gln Arg Leu Met Ser Thr Arg
 20 25 30
 Arg Lys Gly Arg Asn Ser Arg Pro Gly Trp Thr Leu
 35 40

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```

Ser Val Gly Asn Asp Lys Thr Ser Arg Pro Val Ser Phe Tyr Gly Arg
 1           5           10           15
Val Ser Asp Leu Trp Asn Ala Ser Leu Met Pro Lys Arg Thr Pro Ser
          20           25           30
Ser Lys Arg His Asp Asp Gly
          35

```

10

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

15

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```

Arg Trp Pro Ser Val Gly Tyr Lys Gly Asn Gly Ser Asp Thr Ile Asp
 1           5           10           15
Val His Ser Asn Asp Ala Ser Thr Lys Arg Ser Leu Ile Tyr Asn His
          20           25           30
Arg Arg Pro Leu Phe Pro
          35

```

20

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

25

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

```

Arg Thr Phe Glu Asn Asp Gly Leu Gly Val Gly Arg Ser Ile Gln Lys
 1           5           10           15
Lys Ser Asp Arg Trp Tyr Ala Ser His Asn Ile Arg Ser His Phe Ala
          20           25           30
Ser Met Ser Pro Ala Gly Lys
          35

```

30

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

35

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Ser Tyr Cys Arg Val Lys Gly Gly Gly Glu Gly Gly His Thr Asp Ser
 1 5 10 15
 Asn Leu Ala Arg Ser Gly Cys Gly Lys Val Ala Arg Thr Ser Arg Leu
 20 25 30
 Gln His Ile Asn Pro Arg Ala Thr Pro Pro Ser Arg
 35 40

5 (2) INFORMATION FOR SEQ ID NO:34:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 39 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Ser Trp Thr Arg Trp Gly Lys His Thr His Gly Gly Phe Val Asn Lys
 1 5 10 15
 Ser Pro Pro Gly Lys Asn Ala Thr Ser Pro Tyr Thr Asp Ala Gln Leu
 20 25 30
 Pro Ser Asp Gln Gly Pro Pro
 35

15

(2) INFORMATION FOR SEQ ID NO:35:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 44 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

20

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Ser Gln Val Asp Ser Phe Arg Asn Ser Phe Arg Trp Tyr Glu Pro Ser
 1 5 10 15
 Arg Ala Leu Cys His Gly Cys Gly Lys Arg Asp Thr Ser Thr Thr Arg
 20 25 30
 Ile His Asn Ser Pro Ser Asp Ser Tyr Pro Thr Arg
 35 40

25

(2) INFORMATION FOR SEQ ID NO:36:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 39 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

30

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Ser Phe Leu Arg Phe Gln Ser Pro Arg Phe Glu Asp Tyr Ser Arg Thr
 1 5 10 15
 Ile Ser Arg Leu Arg Asn Ala Thr Asn Pro Ser Asn Val Ser Asp Ala
 20 25 30
 His Asn Asn Arg Ala Leu Ala
 35

35

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

```

Arg Ser Ile Thr Asp Gly Gly Ile Asn Glu Val Asp Leu Ser Ser Val
 1           5           10           15
Ser Asn Val Leu Glu Asn Ala Asn Ser His Arg Ala Tyr Arg Lys His
          20           25           30
Arg Pro Thr Leu Lys Arg Pro
          35

```

10

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

```

Ser Ser Lys Val Ser Ser Pro Arg Asp Pro Thr Val Pro Arg Lys Gly
 1           5           10           15
Gly Asn Val Asp Tyr Gly Cys Gly His Arg Ser Ser Ala Arg Met Pro
          20           25           30
Thr Ser Ala Leu Ser Ser Ile Thr Lys Cys Tyr Thr
          35           40

```

20

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

```

Arg Ala Ser Thr Gln Gly Gly Arg Gly Val Ala Pro Glu Phe Gly Ala
 1           5           10           15
Ser Val Leu Gly Arg Gly Cys Gly Ser Ala Thr Tyr Tyr Thr Asn Ser
          20           25           30
Thr Ser Cys Lys Asp Ala Met Gly His Asn Tyr Ser
          35           40

```

30

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Arg Trp Cys Glu Lys His Lys Phe Thr Ala Ala Arg Cys Ser Ala Gly
 1 5 10 15
 Ala Gly Phe Glu Arg Asp Ala Ser Arg Pro Pro Gln Pro Ala His Arg
 20 25 30
 Asp Asn Thr Asn Arg Asn Ala
 35

5 (2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Ser Phe Gln Val Tyr Pro Asp His Gly Leu Glu Arg His Ala Leu Asp
 1 5 10 15
 Gly Thr Gly Pro Leu Tyr Ala Met Pro Gly Arg Trp Ile Arg Ala Arg
 20 25 30
 Pro Gln Asn Arg Asp Arg Gln
 35

15

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Ser Arg Cys Thr Asp Asn Glu Gln Cys Pro Asp Thr Gly Thr Arg Ser
 1 5 10 15
 Arg Ser Val Ser Asn Ala Arg Tyr Phe Ser Ser Arg Leu Leu Lys Thr
 20 25 30
 His Ala Pro His Arg Pro
 35

25

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Ser Ala Arg Asp Ser Gly Pro Ala Glu Asp Gly Ser Arg Ala Val Arg
 1 5 10 15
 Leu Asn Gly Val Glu Asn Ala Asn Thr Arg Lys Ser Ser Arg Ser Asn
 20 25 30
 Pro Arg Gly Arg Arg His Pro
 35

35

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

```

Ser Ser Ala Asp Ala Glu Lys Cys Ala Gly Ser Leu Leu Trp Trp Gly
 1           5           10           15
Arg Gln Asn Asn Ser Gly Cys Gly Ser Pro Thr Lys Lys His Leu Lys
      20           25           30
His Arg Asn Arg Ser Gln Thr Ser Ser Ser Ser His
      35           40

```

10

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

```

Arg Pro Lys Asn Val Ala Asp Ala Tyr Ser Ser Gln Asp Gly Ala Ala
 1           5           10           15
Ala Glu Glu Thr Ser His Ala Ser Asn Ala Ala Arg Lys Ser Pro Lys
      20           25           30
His Lys Pro Leu Arg Arg Pro
      35

```

20

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

```

Arg Gly Ser Thr Gly Thr Ala Gly Gly Glu Arg Ser Gly Val Leu Asn
 1           5           10           15
Leu His Thr Arg Asp Asn Ala Ser Gly Ser Gly Phe Lys Pro Trp Tyr
      20           25           30
30 Pro Ser Asn Arg Gly His Lys
      35

```

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

Arg Trp Gly Trp Glu Arg Ser Pro Ser Asp Tyr Asp Ser Asp Met Asp
 1 5 10 15
 Leu Gly Ala Arg Arg Tyr Ala Thr Arg Thr His Arg Ala Pro Pro Arg
 20 25 30
 Val Leu Lys Ala Pro Leu Pro
 35

5 (2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

Arg Gly Trp Lys Cys Glu Gly Ser Gln Ala Ala Tyr Gly Asp Lys Asp
 1 5 10 15
 Ile Gly Arg Ser Arg Gly Cys Gly Ser Ile Thr Lys Asn Asn Thr Asn
 20 25 30
 His Ala His Pro Ser His Gly Ala Val Ala Lys Ile
 35 40

15

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

Ser Arg Glu Glu Ala Asn Trp Asp Gly Tyr Lys Arg Glu Met Ser His
 1 5 10 15
 Arg Ser Arg Phe Trp Asp Ala Thr His Leu Ser Arg Pro Arg Arg Pro
 20 25 30
 Ala Asn Ser Gly Asp Pro Asn
 35

25

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

Glu Trp Tyr Ser Trp Lys Arg Ser Ser Lys Ser Thr Gly Leu Gly Asp
 1 5 10 15
 Thr Ala Thr Arg Glu Gly Cys Gly Pro Ser Gln Ser Asp Gly Cys Pro
 20 25 30
 Tyr Asn Gly Arg Leu Thr Thr Val Lys Pro Arg Lys
 35 40

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

```

Arg  Glu  Phe  Ala  Glu  Arg  Arg  Leu  Trp  Gly  Cys  Asp  Asp  Leu  Ser  Trp
 1          5          10          15
Arg  Leu  Asp  Ala  Glu  Gly  Cys  Gly  Pro  Thr  Pro  Ser  Asn  Arg  Ala  Val
          20          25          30
Lys  His  Arg  Lys  Pro  Arg  Pro  Arg  Ser  Pro  Ala  Leu
          35          40

```

10

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

15

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

```

Ser  Asp  His  Ala  Leu  Gly  Thr  Asn  Leu  Arg  Ser  Asp  Asn  Ala  Lys  Glu
 1          5          10          15
Pro  Gly  Asp  Tyr  Asn  Cys  Cys  Gly  Asn  Gly  Asn  Ser  Thr  Gly  Arg  Lys
          20          25          30
Val  Phe  Asn  Arg  Arg  Arg  Pro  Ser  Ala  Ile  Pro  Thr
          35          40

```

20

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

25

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

```

Arg  His  Ile  Ser  Glu  Tyr  Ser  Phe  Ala  Asn  Ser  His  Leu  Met  Gly  Gly
 1          5          10          15
Glu  Ser  Lys  Arg  Lys  Gly  Cys  Gly  Ile  Asn  Gly  Ser  Phe  Ser  Pro  Thr
          20          25          30
Cys  Pro  Arg  Ser  Pro  Thr  Pro  Ala  Phe  Arg  Arg  Thr
          35          40

```

30

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

35

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

```

Ser Arg Glu Ser Gly Met Trp Gly Ser Trp Trp Arg Gly His Arg Leu
 1           5           10
Asn Ser Thr Gly Asn Ala Asn Met Asn Ala Ser Leu Pro Pro Asp
      20           25           30
Pro Pro Val Ser Thr Pro
      35

```

5 (2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

```

Ser Thr Pro Pro Ser Arg Glu Ala Tyr Ser Arg Pro Tyr Ser Val Asp
 1           5           10           15
Ser Asp Ser Asp Thr Asn Ala Lys His Ser Ser His Asn Arg Arg Leu
      20           25           30
Arg Thr Arg Ser Arg Pro Asn
      35

```

15

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 177 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

20

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

```

TCTCACTCCT CGAGATCCGG CGCTTATGAG AGTCCGGATG GTCGGGGGGG TCGGAGCTAT      60
GTGGGGGGCG GGGGTGGNTG TGGTAACATT GGTCCGAAGC ATAACCTGTG GGGGCTGCGT      120
ACCGCGTCGC CGGCCTGCTG GGACTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA      177

```

(2) INFORMATION FOR SEQ ID NO:57:

25

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 177 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

```

TCTCACTCCT CGAGTCCTCG CTCTTTCTGG CCCGTTGTGT CCCGGCATGA GTCGTTTGGG      60
ATCTCTAACT ATTTGGGNTG TGGTTATCGT ACATGTATCT CCGGCACGAT GACTAAGTCT      120
AGCCCGATTT ACCCTCGGCA TTCGTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA      177

```

(2) INFORMATION FOR SEQ ID NO:58:

35

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 177 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

TCTCACTCCT	CGAGTAGTAG	CTCCGATTGG	GGTGGTGTGC	CTGGGAAGGT	GGTTAGGGAG	60
CGCTTTAAGG	GGCGCGGTTG	TGGTATTTCC	ATCACCTCCG	TGCTCACTGG	GAAGCCCAAT	120
CCGTGTCCGG	AGCCTAAGGC	GGCCTCTAGA	ATCGAAGGTC	GCGCTAGACC	TTCGAGA	177

5

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 177 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

10

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

TCTCACTCCT	CGAGAGTTGG	CCAGTGCACG	GATTCTGATG	TGCGGCGTCC	TTGGGCCAGG	60
TCTTGCGCTC	ATCAGGGTTG	TGGTGCGGGC	ACTCGCAACT	CGCACGGCTG	CATCACCCGT	120
CCTCTCCGCC	AGGCTAGCGC	TCATTCTAGA	ATCGAAGGTC	GCGCTAGACC	TTCGAGA	177

(2) INFORMATION FOR SEQ ID NO:60:

15

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 162 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

TCTCACTCCT	CGAGCCACTC	CGGTGGTATG	AATAGGCGCT	ACGGGGATGT	GTTTAGGGAG	60
CTTCGTGATC	GGTGGAACGC	CACTTCCCAC	CACACTCGCC	CCACCCCTCA	GCTCCCCCGT	120
GGGCCTAATT	CTAGAATCGA	AGGTCGCGCT	AGACCTTCGA	GA		162

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:

25

- (A) LENGTH: 168 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

30	TCTCACTCCT	CGAGTCCGTG	CGGGGGGTG	TGGGGGCGTT	TTATGCAGGG	TGGCCTTTTC	60
	GGCGGTAGGA	CTGATGGTTG	TGGTGCCCAT	AGAAACCGCA	CTTCTGCGTC	GTTAGAGCCC	120
	CCGAGCAGCG	ACTACTCTAG	AATCGAAGGT	CGCGCTAGAC	CTTCGAGA		168

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:

35

- (A) LENGTH: 135 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

TCTCACTCCT	CGAGGGGCGC	CGCCGATCAG	CGGCGGGGGT	GGTCCGAGAA	CTTGGGGTTG	60
CCTAGGGTGG	GGTGGGACGC	CATCGCTCAC	AATAGCTATA	CGTTCACCTC	GCGCCGCCCG	120
CGCCCCCCT	CTAGA					135

(2) INFORMATION FOR SEQ ID NO:63:

5

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 177 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

TCTCACTCCT	CGAGCGGTGG	GGAGGTCAGC	TCCTGGGGCC	GCGTGAATGA	CCTCTGCGCT	60
AGGGTGAGTT	GGACTGGTTG	TGGTACTGCT	CGTTCCGCGC	GTACCGACAA	CAAAGGCTTT	120
CTTCCTAAGC	ACTCGTCACT	CCGCTCTAGA	ATCGAAGGTC	GCGCTAGACC	TTCGAGA	177

(2) INFORMATION FOR SEQ ID NO:64:

15

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 177 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

20

TCTCACTCCT	CGAGTGATAG	TGACGGGGAT	CATTATGGGC	TTCGGGGGGG	GGTGCGTTGT	60
TCGCTTCGTG	ATAGGGGTTG	TGGTCTGGCC	CTGTCCACCG	TCCATGCTGG	TCCCCCTCT	120
TTTTACCCA	AGCTCTCCAG	CCCCTCTAGA	ATCGAAGGTC	GCGCTAGACC	TTCGAGA	177

(2) INFORMATION FOR SEQ ID NO:65:

25

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 162 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

30

TCTCACTCCT	CGAGGAGCTT	GGGTAATTAT	GGCGTCACCG	GGACTGTGGA	CGTGACGGTT	60
TTGCCCATGC	CTGGCCACGC	CAACCACCTT	GGTGTCTCCT	CCGCCTCTAG	CTCTGATCCT	120
CCGCGGCGCT	CTAGAATCGA	AGGTCGCGCT	AGACCTTCGA	GA		162

(2) INFORMATION FOR SEQ ID NO:66:

35

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 159 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

TCTCACTCCT CGAGAACTAC GACGGCTAAG GGGTGTCTTC TCGGAAGCTT CGGCGTTCTT 60
 AGTGGGTGCT CATTTACGCC AACCTCTCCA CCGCCCCACC TAGGATACCC CCCCCACTCC 120
 GTCAATTCTA GAATCGAAGG TCGCGCTAGA CCTTCGAGA 159

(2) INFORMATION FOR SEQ ID NO:67:

- 5 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 162 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

10 TCTCACTCCT CGAGCCCGAA GTTGTCCAGC GTGGGTGTTA TGAATAAGGT CACGGAGCTG 60
 CCCACGGAGG GGCCTAACGC CATTAGTATT CCGATCTCCG CGACCCTCGG CCCGCGCAAC 120
 CCGCTCCGCT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA 162

(2) INFORMATION FOR SEQ ID NO:68:

- 15 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 162 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

20 TCTCACTCCT CGAGGTGGTG CGGCGCTGAG CTGTGCAACT CGGTGACTAA GAAGTTTCGC 60
 CCGGGCTGGC GGGATCACGC CAATCCCTCC ACCCATCATC GTACTCCCC GCCCAGCCAG 120
 TCCAGCCCTT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA 162

(2) INFORMATION FOR SEQ ID NO:69:

- 25 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 176 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

30 TCTCACTCCT CGAGGTGGTG CGGCGCTGAT GACCCGTGTG GTGCCAGTCG TTGGCGGGGG 60
 GGCAACAGCT TGTTTGTTG TGGTCTTCGT TGTAGTGC GG CAGAGCAC CCCGAGTGGC 120
 AGGATCCATT CCACTTCGAC CAGCTCTAGA ATCGAAGGTG CGCTAGACCT TCGAGA 176

(2) INFORMATION FOR SEQ ID NO:70:

- 35 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 162 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

TCTCACTCCT CGAGTAAGTC CGGGGAGGGG GGTGACAGTA GCAGGGGCGA GACGGGCTGG 60
 GCGAGGGTTC GGTCTCACGC CATGACTGCT GGCCGCTTTC GGTGGTACAA CCAGTTGCCC 120

TCTGATCGGT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA

162

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 159 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

TCTCACTCCT CGAGGTCGAG CGCCAATAAT TGCAGGTGGA AGTCTGATTG GATGCGCAGG 60
GCCTGTATTG CTCGTTACGC CAACAGTTTCG GGCCCCGCCC GCGCCGTCGA CACTAAGGCC 120
10 GCGCCCTCTA GAATCGAAGG TCGCGCTAGA CCTTCGAGA 159

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 177 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

TCTCACTCCT CGAGTAAGTG GTCGTGGAGT TCGAGGTGGG GCTCCCCGCA GGATAAGGTT 60
GAGAAGACCA GGGCGGGTTG TGGTGGTAGT CCCAGCAGCA CCAATTGTCA CCCCTACACC 120
TTTGGCCCCC CCCC GCAAGC CGCTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA 177

20

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 177 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

TCTCACTCCT CGAGTGGGTT CTGGGAGTTT AGCAGGGGGC TTTGGGATGG GGAGAACCGT 60
AAGAGTGTCC GGTGCGGTTG TGGTTTTCTG GGCTCCTCTG CTCAGGGCCC GTGTCCGGTC 120
ACGCCTGCCA CCATTGACAA AACTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA 177

(2) INFORMATION FOR SEQ ID NO:74:

30

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 177 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

35

TCTCACTCCT CGAGTGAGAG CGGGCGGTGC CGTAGCGTGA GCCGGTGGAT GACGACGTGG 60
CAGACGCAGA AGGGCGGTTG TGGTTCCAAT GTTTCCCGCG GTTCGCCCCT CGACCCCTCT 120
CACCAGACCG GGCATGCCAC TACTTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA 177

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 162 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

TCTCACTCCT	CGAGGGAGTG	GAGGTTTGCC	GGGCCGCCGT	TGGACCTGTG	GGCGGGTCCG	60
AGCTTGCCCT	CTTTTAACGC	CAGTTCCCAC	CCTCGCGCCC	TGCGCACCTA	TTGGTCCCAG	120
CGGCCCCGCT	CTAGAAATCGA	AGGTCGCGCT	AGACCTTCGA	GA		162

10

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 177 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

TCTCACTCCT	CGAGGATGGA	GGACATCAAG	AACTCGGGGT	GGAGGGACTC	TTGTAGGTGG	60
GGTGACCTGA	GGCCTGGTTG	TGGTAGCCGC	CAGTGGTACC	CCTCGAATAT	GCGTTCTAGC	120
AGAGATTACC	CCGCGGGGGG	CCACTCTAGA	ATCGAAGGTC	GCGCTAGACC	TTCGAGA	177

(2) INFORMATION FOR SEQ ID NO:77:

20

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 152 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

25

TCTCACTCCT	CGAGTCATCC	GTGGTACAGG	CATTGGAACC	ATGGTGACTT	CTCTGGTTCCG	60
GGCCAGTCAC	GCCACACCCC	GCCGGAGAGC	CCCCACCCCG	GCCGCCCTAA	TGCCACCATT	120
TCTAGAATCG	AAGGTCGCGC	TAGACCTTCG	AG			152

(2) INFORMATION FOR SEQ ID NO:78:

30

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 177 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

TCTCACTCCT	CGAGATATAA	GCACGATATC	GGTTGCGATG	CTGGGGTTGA	CAAGAAGTCG	60
TCGTCTGTGC	GTGGTGTTG	TGGTGCTCAT	TNGTCGCCAC	CCCGCGCCCG	CCGTGGTCTT	120
CGCGGCACGA	TGGTTAGCAG	GCTTTCTAGA	ATCGAAGGTC	GCGCTAGACC	TTCGAGA	177

(2) INFORMATION FOR SEQ ID NO:79:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 177 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- 5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:
- | | | | | | | |
|------------|------------|------------|------------|------------|------------|-----|
| TCTCACTCCT | CGAGTCAGGG | CTCCAAGCAG | TGTATGCAGT | ACCGCACCGG | TCGTTTGACG | 60 |
| GTGGGGTCTG | AGTATGGTTG | TGGTATGAAC | CCCGCCCGCC | ATGCCACGCC | CGCTTATCCG | 120 |
| GCGCGCCTGC | TGCCACGCTA | TCGCTCTAGA | ATCGAAGGTC | GCGCTAGACC | TTCGAGA | 177 |
- (2) INFORMATION FOR SEQ ID NO:80:
- 10 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 177 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:
- | | | | | | | | |
|---------------|------------|-------------|------------|------------|------------|------------|-----|
| 15 TCTCACTCCT | CGAGTGGGCG | GA | CTACTAGT | GAGATTTCTG | GGCTCTGGGG | TTGGGGTGAC | 60 |
| GACCGGAGCG | GTTATGGTTG | GGGTAACACG | CTCCGCCCCA | ACTACATCCC | TTATAGGCAG | | 120 |
| GCGACGAACA | GGCATCGTTA | TACGTCCTAGA | ATCGAAGGTC | GCGCTAGACC | TTCGAGA | | 177 |
- (2) INFORMATION FOR SEQ ID NO:81:
- 20 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 162 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:
- | | | | | | | |
|---------------|------------|------------|------------|------------|------------|-----|
| 25 TCTCACTCCT | CGAGGTGGAA | TTGGACTGTC | TTGCCCCGCA | CTGGCGGGCA | TTACTGGACG | 60 |
| CGTTTCGACG | ACTATCACGC | CATTAACAAT | CACAGGCCGA | GCATCCCCCA | CCAGCATCCG | 120 |
| ACCCCTATCT | CTAGAATCGA | AGGTCGCGCT | AGACCTTCGA | GA | | 162 |
- (2) INFORMATION FOR SEQ ID NO:82:
- 30 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 177 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:
- | | | | | | | |
|---------------|------------|-------------|------------|------------|------------|-----|
| 35 TCTCACTCCT | CGAGTTGGTC | GTCGTGGAAT | TGGAGCTCTA | AGACTACTCG | TCTGGGCGAC | 60 |
| AGGGCGACTC | GGGAGGGTTG | TGGTCCCAGC | CAGTCTGATG | GCTGTCCTTA | TAACGGCCGC | 120 |
| CTTACGACCG | TCAAGCCTCG | CACGTCCTAGA | ATCGAAGGTC | GCGCTAGACC | TTCGAGA | 177 |
- (2) INFORMATION FOR SEQ ID NO:83:
- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 156 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

5 TCTCACTCCT CGAGTGGTAG TTTGAACGCA TGGCAACCGC GGTCATGGGT GGGGGGCGCG 60
TTCCGTCAC ACGCCAACAA TAACTTGAAC CCCAAGCCCA CCATGGTTAC TNGTCACCCT 120
ACCTCTAGAA TCGAAGGTCG CGCTAGACCT TCGAGA 156

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:

10 (A) LENGTH: 178 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

15 TCTCACTCCT CGAGGTATTC GGGTTTGTCC CCGCGGGACA ACGGTCCCGC TTGTAGTCAG 60
GAGGCTACCT TGGAGGGTTG TGGTGCAGAG AGGCTGATGT CCACCCGTCG CAAGGGCCGC 120
AACTCCCGCC CCGGGTGGAC GCTCTCTAGA ATCGAAGGTC GCGCTAGACC CTTTCGAGA 178

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:

20 (A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

25 TCTCACTCCT CGAGCGTGGG GAATGATAAG ACTAGCAGGC CGGTTTCCTT CTACGGGCGC 60
GTTAGTGATC TGTGGAACGC CAGCTTGATG CCGAAGCGTA CTCCCAGCTC GAAGCGCCAC 120
GATGATGGCT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA 162

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:

30 (A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

TCTCACTCCT CGAGTACTCC CCCAGTAGG GAGGCGTATA GTAGGCCCTA TAGTGTCGAT 60
AGCGATTGCG ATACGAACGC CAAGCACAGC TCCACAACC GCCGTNTGCG GACGCGCAGC 120
CGCCCGAAT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA 162

(2) INFORMATION FOR SEQ ID NO:87:

35 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 159 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

5 TCTCACTCCT CGAGATGGCC TAGTGTGGGT TACAAGGGTA ATGGCAGTGA CACTATTGAT 60
GTTACAGCA ATGACGCCAG TACTAAGAGG TCCCTCATCT ATAACCACCG CCGCCCCNTC 120
TTTCCCTCTA GAATCGAAGG TCGCGCTAGA CCTTCGAGA 159

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 162 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

10 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

15 TCTCACTCCT CGAGAACGTT TGAGAACGAC GGGCTGGGCG TCGGCCGGTC TATTCAGAAG 60
AAGTCGGATA GGTGGTACGC CAGCCACAAC ATTCGTAGCC ATTCGCGTC CATGTCTCCC 120
GCTGGTAAGT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA 162

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 160 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

20 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

TCTCACTCCT CGAGCTATTG TCGGGTTAAG GGTGGTGGGG AGGGGGGGCA TACGGATTCC 60
AATCTGGCTA GGTCCGGTTG TGTAAGGTG GCCAGGACCA GCAGGCTTCA GCATATCAAC 120
CCGCGCGCTA CCCCCCCTC CCGGTCTAGA ATCGAAGGTC 160

(2) INFORMATION FOR SEQ ID NO:90:

25

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 162 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

TCTCACTCCT CGAGTTGGAC TCGGTGGGGC AAGCACANTC ATGGGGGGTT TGTGAACAAG 60
TCTCCCCCTG GGAAGAACGC CACGAGCCCC TACACCGACG CCCAGCTGCC CAGTGATCAG 120
GGTCCTCCCT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA 162

(2) INFORMATION FOR SEQ ID NO:91:

35 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 177 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

TCTCACTCCT	CGAGTCAGGT	TGATTCGTTT	CGTAATAGCT	TTCGGTGGTA	TGAGCCGAGC	60
AGGGCTCTGT	GCCATGGTTG	TGGTAAGCGC	GACACCTCCA	CCACTCGTAT	CCACAATAGC	120
CCCAGCGACT	CCTATCCTAC	ACGCTCTAGA	ATCGAAGGTC	GCGCTAGACC	TTCGAGA	177

5

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 162 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

10

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

TCTCACTCCT	CGAGCTTTTT	GCGTTTCCAG	AGTCCGAGGT	TCGAGGATTA	CAGTAGGACG	60
ATCTNTCGGT	TGCGCAACGC	CACGAACCCG	AGTAATGTCT	CCGATGCGCA	CAATAACCCG	120
GCCTTGCCCT	CTAGAATCGA	AGGTCGCGCT	AGACCTTCGA	GA		162

(2) INFORMATION FOR SEQ ID NO:93:

15

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 162 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

TCTCACTCCT	CGAGGAGCAT	CACCGACGGG	GGCATCAATG	AGGTGGACCT	GAGTAGTG TG	60
TCGAACGTTT	TTGAGAACGC	CAACTCGCAT	AGGGCCTACA	GGAAGCATCG	CCCGACCTTG	120
AAGCGTCCTT	CTAGAATCGA	AGGTCGCGCT	AGACCTTCGA	GA		162

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:

25

- (A) LENGTH: 177 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

30	TCTCACTCCT	CGAGTTCGAA	GGTGAGCAGC	CCGAGGGATC	CGACGGTCCC	GCGGAAGGGC	60
	GGCAATGTTG	ATTATGGTTG	TGGTCACAGG	TCTTCCGCCC	GGATGCCTAC	CTCCGCTCTG	120
	TCGTCGATCA	CGAAGTGCTA	CACTTCTAGA	ATCGAAGGTC	GCGCTAGACC	TTCGAGA	177

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:

35

- (A) LENGTH: 177 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

TCTCACTCCT	CGAGAGCCAG	TANGCAGGGC	GGCCGGGGTG	TTGCCCTGA	GTTTGGGGCG	60
AGCGTTTTTG	GTNGTGGTTG	TGGTAGCGCC	ACTTATTACA	CGAACTCCAC	CAGCTGCAAG	120
GATGCTATGG	GCCACAATA	CTCGTCTAGA	ATCGAAGGTC	GCGNTAGACC	TTCGAGA	177

(2) INFORMATION FOR SEQ ID NO:96:

5

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 162 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

TCTCACTCCT	CGAGATGGTG	CGAGAAGCAC	AAGTTTACGG	CTGCGCGTTG	CAGCGCGGGG	60
GCGGGTTTTG	AGAGGGANGC	CAGCCGTCCG	CCCCAGCCTG	CCCACCGGGA	TAATACCAAC	120
CGTAATGCNT	NTAGAATCGA	AGGTCGCGCT	AGACCTTCGA	GA		162

(2) INFORMATION FOR SEQ ID NO:97:

15

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 162 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

20

TCTCACTCCT	CGAGTTTTC	GGTGTACCCG	GACCATGGTC	TGGAGAGGCA	TGCTTTGGAC	60
GGGACGGGTC	CGCTTTACGC	CATGCCCGGC	CGCTGGATTA	GGGCGCGTCC	GCAGAACAGG	120
GACCGCCAGT	CTAGAATCGA	AGGTCGCGCT	AGACCTTCGA	GA		162

(2) INFORMATION FOR SEQ ID NO:98:

25

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 159 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

30

TCTCACTCCT	CGAGCAGGTG	TACGGACAAC	GAGCAGTGCC	CCGATACCGG	GANTAGGTCT	60
CGTTCCGTTA	GTAACGCCAG	GTACTTTTCG	AGCAGGTTGC	TCAAGACTCA	CGCCCCCAT	120
CGCCCTTCTA	GAATCGAAGG	TCGCGCTAGA	CCTTCGAGA			159

(2) INFORMATION FOR SEQ ID NO:99:

35

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 162 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

TCTCACTCCT CGAGTGCCAG GGATAGCGGG CCTGCGGAGG ATGGGTCCCG CGCCGTCCGG 60
 TTGAACGGGG TTGAGAACGC CAACACTAGG AAGTCCTCCC GCAGTAACCC GCGGGGTAGG 120
 CGCCATCCCT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA 162

(2) INFORMATION FOR SEQ ID NO:100:

- 5 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 177 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

10 TCTCACTCCT CGAGTTCCGC CGATGCGGAG AAGTGTGCGG GCAGTCTGTT GTGGTGGGGT 60
 AGGCAGAACACTCCGGTTG TGGTTCGCCC ACGAAGAAGC ATCTGAAGCA CCGCAATCGC 120
 AGTCAGACCT CCTCTTCGTC CCACTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA 177

(2) INFORMATION FOR SEQ ID NO:101:

- 15 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 162 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

20 TCTCACTCCT CGAGACCGAA GAACGTGGCC GATGCTTATT CGTCTCAGGA CGGGGCGGCG 60
 GCCGAGGAGA CGTCTCACGC CAGTAATGCC GCGCGGAAGT CCCCTAAGCA CAAGCCCTTG 120
 AGGCGGCCTT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA 162

(2) INFORMATION FOR SEQ ID NO:102:

- 25 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 162 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

TCTCACTCCT CGAGAGGCAG TACGGGGACG GCCGGCGGCG AGCGTTCCGG GGTGCTCAAC 60
 CTGCACACCA GGGATAACGC CAGCGGCAGC GGTTCCTAAC CGTGGTACCC TTCGAATCGG 120
 GGTCACAAGT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA 162

30 (2) INFORMATION FOR SEQ ID NO:103:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 162 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

TCTCACTCCT CGAGGTGGGG GTGGGAGAGG AGTCCGTCCG ACTACGATTC TGATATGGAC 60
 TTGGGGGCGA GGAGGTACGC CACCCGCACC CACCGCGCGC CCCCTCGCGT CTTGAAGGCT 120

CCCCTGCCCT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA

162

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

10 TCTCACTCCT CGAGGCACTG GAAGTGCAGG GGCTCTCAGG CTGCCTACGG GGACAAGGAT 60
ATCGGGAGGT CCAGGGGTTG TGGTTCCATT ACAAAGAATA ACACATAATCA CGCCCATCCT 120
AGCCACGGCG CCGTTGCTAA GATCTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA 177

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

20 TCTCACTCCT CGAGCCGCGA GGAGGCGAAC TGGGACGGCT ATAAGAGGGA GATGAGCCAC 60
CGGAGTCGCT TTTGGGACGC CACCCACCTG TCCCGCCCTC GCCGCCCCGC TAACTCTGGT 120
GACCCTAACT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA 162

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

30 TCTCACTCNT CGAGAGAGTT CGCGGAGAGG AGGTTGTGGG GGTGTGATGA CCTGAGTTGG 60
CGTCTCGACG CGGAGGGTTG TGGTCCCACT CCGAGCAATC GGGCCGTCAA GCATCGCAAG 120
CCCCGCCCAC GCTCCCCCGC ACTCTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA 177

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:

- 35 (A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

35 TCTCACTCNT NGAGTGATCA CGCGTTGGGG ACGAATCTGA GGTCTGACAA TGCCAAGGAG 60
CCGGGTGATT ACAACTGTTG TGGTAACGGG AACTCTACCG GGCGAAAGGT TTTTAACCGT 120
AGGCGCCCCT CCGCCATCCC CANTTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA 177

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 177 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

```

TCTCACTCCT CGAGGCATAT TTCTGAGTAT AGCTTTGCGA ATTCCCACTT GATGGGTGGC      60
GAGTCCAAGC GGAAGGGTTG TGGTATTAAC GGCTCCTTTT CTCCCACTTG TCCCCGCTCC      120
CCCACCCAG CCTTCGCGCG CACCTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA      177

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10

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 158 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

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TCTCACTCCT CGAGCCGGGA GAGCGGGATG TGGGGTAGTT GGTGGCGTGG TCACAGGTTG      60
AATTCCAAGG GGGGTAACGC CAACATGAAT GCTAGTCTGC CCCCCGACCC CCCTGTTTCC      120
ACTCCGTCTA GAATCGAAGG TCGCGCTAGA CCTTCGAG      158

```

(2) INFORMATION FOR SEQ ID NO:110:

20

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 708 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

25

```

Met Gly Met Ser Lys Ser His Ser Phe Phe Gly Tyr Pro Leu Ser Ile
 1           5           10           15
Phe Phe Ile Val Val Asn Glu Phe Cys Glu Arg Phe Ser Tyr Tyr Gly
 20           25           30
Met Arg Ala Ile Leu Ile Leu Tyr Phe Thr Asn Phe Ile Ser Trp Asp
 35           40           45
Asp Asn Leu Ser Thr Ala Ile Tyr His Thr Phe Val Ala Leu Cys Tyr
 50           55           60
30 Leu Thr Pro Ile Leu Gly Ala Leu Ile Ala Asp Ser Trp Leu Gly Lys
 65           70           75           80
Phe Lys Thr Ile Val Ser Leu Ser Ile Val Tyr Thr Ile Gly Gln Ala
 85           90           95
Val Thr Ser Val Ser Ser Ile Asn Asp Leu Thr Asp His Asn His Asp
100           105           110
Gly Thr Pro Asp Ser Leu Pro Val His Val Val Leu Ser Leu Ile Gly
115           120           125
35 Leu Ala Leu Ile Ala Leu Gly Thr Gly Gly Ile Lys Pro Cys Val Ser
130           135           140
Ala Phe Gly Gly Asp Gln Phe Glu Glu Gly Gln Glu Lys Gln Arg Asn
145           150           155           160
Arg Phe Phe Ser Ile Phe Tyr Leu Ala Ile Asn Ala Gly Ser Leu Leu
165           170           175

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	Ser	Thr	Ile	Ile	Thr	Pro	Met	Leu	Arg	Val	Gln	Gln	Cys	Gly	Ile	His
				180					185					190		
	Ser	Lys	Gln	Ala	Cys	Tyr	Pro	Leu	Ala	Phe	Gly	Val	Pro	Ala	Ala	Leu
			195					200					205			
	Met	Ala	Val	Ala	Leu	Ile	Val	Phe	Val	Leu	Gly	Ser	Gly	Met	Tyr	Lys
			210				215					220				
5	Lys	Phe	Lys	Pro	Gln	Gly	Asn	Ile	Met	Gly	Lys	Val	Ala	Lys	Cys	Ile
						230					235				240	
	Gly	Phe	Ala	Ile	Lys	Asn	Arg	Phe	Arg	His	Arg	Ser	Lys	Ala	Phe	Pro
					245					250					255	
	Lys	Arg	Glu	His	Trp	Leu	Asp	Trp	Ala	Lys	Glu	Lys	Tyr	Asp	Glu	Arg
				260					265					270		
	Leu	Ile	Ser	Gln	Ile	Lys	Met	Val	Thr	Arg	Val	Met	Phe	Leu	Tyr	Ile
			275					280					285			
	Pro	Leu	Pro	Met	Phe	Trp	Ala	Leu	Phe	Asp	Gln	Gln	Gly	Ser	Arg	Trp
			290				295					300				
10	Thr	Leu	Gln	Ala	Thr	Thr	Met	Ser	Gly	Lys	Ile	Gly	Ala	Leu	Glu	Ile
						310					315				320	
	Gln	Pro	Asp	Gln	Met	Gln	Thr	Val	Asn	Ala	Ile	Leu	Ile	Val	Ile	Met
					325					330					335	
	Val	Pro	Ile	Phe	Asp	Ala	Val	Leu	Tyr	Pro	Leu	Ile	Ala	Lys	Cys	Gly
				340					345					350		
	Phe	Asn	Phe	Thr	Ser	Leu	Lys	Lys	Met	Ala	Val	Gly	Met	Val	Leu	Ala
			355					360					365			
15	Ser	Met	Ala	Phe	Val	Val	Ala	Ala	Ile	Val	Gln	Val	Glu	Ile	Asp	Lys
			370				375					380				
	Thr	Leu	Pro	Val	Phe	Pro	Lys	Gly	Asn	Glu	Val	Gln	Ile	Lys	Val	Leu
						390					395				400	
	Asn	Ile	Gly	Asn	Asn	Thr	Met	Asn	Ile	Ser	Leu	Pro	Gly	Glu	Met	Val
					405					410					415	
	Thr	Leu	Gly	Pro	Met	Ser	Gln	Thr	Asn	Ala	Phe	Met	Thr	Phe	Asp	Val
				420					425					430		
	Asn	Lys	Leu	Thr	Arg	Ile	Asn	Ile	Ser	Ser	Pro	Gly	Ser	Pro	Val	Thr
			435					440					445			
20	Ala	Val	Thr	Asp	Asp	Phe	Lys	Gln	Gly	Gln	Arg	His	Thr	Leu	Leu	Val
			450				455					460				
	Trp	Ala	Pro	Asn	His	Tyr	Gln	Val	Val	Lys	Asp	Gly	Leu	Asn	Gln	Lys
						470					475				480	
	Pro	Glu	Lys	Gly	Glu	Asn	Gly	Ile	Arg	Phe	Val	Asn	Thr	Phe	Asn	Glu
					485					490					495	
	Leu	Ile	Thr	Ile	Thr	Met	Ser	Gly	Lys	Val	Tyr	Ala	Asn	Ile	Ser	Ser
				500					505					510		
25	Tyr	Asn	Ala	Ser	Thr	Tyr	Gln	Phe	Pro	Ser	Gly	Ile	Lys	Gly	Phe	
			515					520					525			
	Thr	Ile	Ser	Ser	Thr	Glu	Ile	Pro	Pro	Gln	Cys	Gln	Pro	Asn	Phe	Asn
						530		535				540				
	Thr	Phe	Tyr	Leu	Glu	Phe	Gly	Ser	Ala	Tyr	Thr	Tyr	Ile	Val	Gln	Arg
						550				555					560	
	Lys	Asn	Asp	Ser	Cys	Pro	Glu	Val	Lys	Val	Phe	Glu	Asp	Ile	Ser	Ala
					565					570					575	
	Asn	Thr	Val	Asn	Met	Ala	Leu	Gln	Ile	Pro	Gln	Tyr	Phe	Leu	Leu	Thr
				580					585					590		
30	Cys	Gly	Glu	Val	Val	Phe	Ser	Val	Thr	Gly	Leu	Glu	Phe	Ser	Tyr	Ser
			595					600					605			
	Gln	Ala	Pro	Ser	Asn	Met	Lys	Ser	Val	Leu	Gln	Ala	Gly	Trp	Leu	Leu
							615					620				
	Thr	Val	Ala	Val	Gly	Asn	Ile	Ile	Val	Leu	Ile	Val	Ala	Gly	Ala	Gly
						630					635				640	
	Gln	Phe	Ser	Lys	Gln	Trp	Ala	Glu	Tyr	Ile	Leu	Phe	Ala	Ala	Leu	Leu
					645					650					655	
	Leu	Val	Val	Cys	Val	Val	Phe	Ala	Ile	Met	Ala	Arg	Phe	Tyr	Thr	Tyr
				660					665					670		
35	Ile	Asn	Pro	Ala	Glu	Ile	Glu	Ala	Gln	Phe	Asp	Glu	Asp	Glu	Lys	Lys
			675					680					685			
	Asn	Arg	Leu	Glu	Lys	Ser	Asn	Pro	Tyr	Phe	Met	Ser	Gly	Ala	Asn	Ser
			690				695					700				

Gln Lys Gln Met
705

(2) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

TCCGGACTCT CATAAGCGCC GG

22

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

ACAACGGGCC AGAAAGAGCG AG

22

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

ACACCACCCC AATCGGAGCT AC

22

(2) INFORMATION FOR SEQ ID NO:114:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

TCAGAATCCG TGCACTGGCC AA

22

(2) INFORMATION FOR SEQ ID NO:115:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

GCCCTATTCA TACCACCGGA GT 22

(2) INFORMATION FOR SEQ ID NO:116:

5 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

CATCAGTCCT ACCGCCGAAA AG 22

(2) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

15 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

CGTATAGCTA TTGTGAGCGA TG 22

(2) INFORMATION FOR SEQ ID NO:118:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

ACGCGCGGAA CGAGCAGTAC CA 22

(2) INFORMATION FOR SEQ ID NO:119:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

30 (B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

CCATAATGAT CCCCCTCACT AT 22

(2) INFORMATION FOR SEQ ID NO:120:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

5 AGACACCCCT TAGCCGTCGT AG 22

(2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
10 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

AGCTCCGTGA CCTTAGTCAT AA 22

(2) INFORMATION FOR SEQ ID NO:122:

15 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

TGCACAGCTC AGCGCCGCAC CA 22

(2) INFORMATION FOR SEQ ID NO:123:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
25 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

ACGGGTCATC AGCGCCGCAC CA 22

30 (2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

TGTCACCCCC CTCCCCGGAC TT 22

- (2) INFORMATION FOR SEQ ID NO:125:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 5 (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:
- ACTCGCAATT ATTGGCGCTC GA 22
- (2) INFORMATION FOR SEQ ID NO:126:
- 10 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:
- 15 GTCTTCTCAA CCTTATCCTG CG 22
- (2) INFORMATION FOR SEQ ID NO:127:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 20 (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:
- AAAGCCCCCT GCTAAACTCC CA 22
- (2) INFORMATION FOR SEQ ID NO:128:
- 25 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:
- 30 CTGCGTCTGC CACGTCGTCA TC 22
- (2) INFORMATION FOR SEQ ID NO:129:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 35 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:
GTTAAAAGAG GGCAAGCTCG GA 22

(2) INFORMATION FOR SEQ ID NO:130:

(i) SEQUENCE CHARACTERISTICS:
5 (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:
10 CCGAGTTCTT GATGTCCTCC AT 22

(2) INFORMATION FOR SEQ ID NO:131:

(i) SEQUENCE CHARACTERISTICS:
15 (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:
TCCAATGCCT GTACCACGGA TG 22

(2) INFORMATION FOR SEQ ID NO:132:

(i) SEQUENCE CHARACTERISTICS:
20 (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:
25 TCGCAACCGA TATCGTGCTT AT 22

(2) INFORMATION FOR SEQ ID NO:133:

(i) SEQUENCE CHARACTERISTICS:
30 (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:
TGCATACACT GCTTGGAGCC CT 22

(2) INFORMATION FOR SEQ ID NO:134:

(i) SEQUENCE CHARACTERISTICS:
35 (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:
- 5 GAAATCTCAC TAGTAGTCCG CC 22
- (2) INFORMATION FOR SEQ ID NO:135:
- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- 10 (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:
- GCGGGCAAGA CAGTCCAATT CC 22
- (2) INFORMATION FOR SEQ ID NO:136:
- (i) SEQUENCE CHARACTERISTICS:
- 15 (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:
- 20 GAGCTCCAAT TCCACGACGA CC 22
- (2) INFORMATION FOR SEQ ID NO:137:
- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- 25 (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:
- GGTTGCCATG CGTTCAAAC ACT 22
- (2) INFORMATION FOR SEQ ID NO:138:
- (i) SEQUENCE CHARACTERISTICS:
- 30 (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:138:
- 35 TCCCGCGGGG ACAAACCCGA AT 22
- (2) INFORMATION FOR SEQ ID NO:139:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 22 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- 5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:
CTGCTAGTCT TATCATTCCC CA 22
- (2) INFORMATION FOR SEQ ID NO:140:
- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 22 base pairs
10 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:
CTATCGACAC TATAGGGCCT AC 22
- 15 (2) INFORMATION FOR SEQ ID NO:141:
- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 22 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- 20 (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:141:
TACCCTTGTA ACCCACAATA GG 22
- (2) INFORMATION FOR SEQ ID NO:142:
- (i) SEQUENCE CHARACTERISTICS:
25 (A) LENGTH: 22 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:
30 TTCTTCTGAA TAGACCGGCC GA 22
- (2) INFORMATION FOR SEQ ID NO:143:
- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 22 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
35 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:143:

- CCACCACCCT TAACCCGACA AT 22
- (2) INFORMATION FOR SEQ ID NO:144:
- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:144:
- AGGGGGAGAC TTGTTCAACAA AC 22
- (2) INFORMATION FOR SEQ ID NO:145:
- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:145:
- CGGCTCATAC CACCGAAAGC TA 22
- (2) INFORMATION FOR SEQ ID NO:146:
- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:146:
- ATCGTCCTAC TGTAATCCTC GA 22
- (2) INFORMATION FOR SEQ ID NO:147:
- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:147:
- GACACACTAC TCAGGTCCAC CT 22
- (2) INFORMATION FOR SEQ ID NO:148:
- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:148:
CCATAATCAA CATTGCCGCC CT 22
- (2) INFORMATION FOR SEQ ID NO:149:
- (i) SEQUENCE CHARACTERISTICS:
5 (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:149:
10 CAAAACGCTC GCCCAAAC CA 22
- (2) INFORMATION FOR SEQ ID NO:150:
- (i) SEQUENCE CHARACTERISTICS:
15 (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:150:
GTAAACTTGT GCTTCTCGCA CC 22
- (2) INFORMATION FOR SEQ ID NO:151:
- (i) SEQUENCE CHARACTERISTICS:
20 (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:151:
25 CCATGGTCCG GGTACACCTG AA 22
- (2) INFORMATION FOR SEQ ID NO:152:
- (i) SEQUENCE CHARACTERISTICS:
30 (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:152:
GTTACTAACG GAACGAGACC TA 22
- (2) INFORMATION FOR SEQ ID NO:153:
- (i) SEQUENCE CHARACTERISTICS:
35 (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:153:
- 5 TGTGCGCGTT CTCAACCCCG TT 22
- (2) INFORMATION FOR SEQ ID NO:154:
- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- 10 (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:154:
- ACAACCGGAG TTGTTCTGCC TA 22
- (2) INFORMATION FOR SEQ ID NO:155:
- (i) SEQUENCE CHARACTERISTICS:
- 15 (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:155:
- 20 TAAGCATCGG CCACGTTCTT CG 22
- (2) INFORMATION FOR SEQ ID NO:156:
- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- 25 (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:156:
- TTATCCCTGG TGTGCAGGTT GA 22
- (2) INFORMATION FOR SEQ ID NO:157:
- (i) SEQUENCE CHARACTERISTICS:
- 30 (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:157:
- 35 TATCAGAATC GTAGTCGGAC GG 22
- (2) INFORMATION FOR SEQ ID NO:158:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 22 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- 5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:158:
CTTTGTAATG GAACCACAAC CC 22
- (2) INFORMATION FOR SEQ ID NO:159:
- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 22 base pairs
10 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:159:
CGGTGGCTCA TCTCCCTCTT AT 22
- 15 (2) INFORMATION FOR SEQ ID NO:160:
- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 22 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:160:
ATCAGACTGG CTGGGACCAC AA 22
- (2) INFORMATION FOR SEQ ID NO:161:
- (i) SEQUENCE CHARACTERISTICS:
25 (A) LENGTH: 22 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:161:
30 CACAACCTCC TCTCCGCGAA CT 22
- (2) INFORMATION FOR SEQ ID NO:162:
- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 22 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
35 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:162:

- AGATTCGTCC CCAACGCGTG AT 22
- (2) INFORMATION FOR SEQ ID NO:163:
- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:163:
- GGGAATTCGC AAAGCTATAC TC 22
- (2) INFORMATION FOR SEQ ID NO:164:
- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:164:
- CCCCGTGGAA TTCAACCTGT GA 22
- (2) INFORMATION FOR SEQ ID NO:165:
- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:165:
- GTCGTCTTTC CAGACGT 17
- (2) INFORMATION FOR SEQ ID NO:166:
- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:166:
- CTTGCGATGCC TGCAGGTCGA C 21
- (2) INFORMATION FOR SEQ ID NO:167:
- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 37 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:167:

Arg Ile Ala Gly Leu Pro Trp Tyr Arg Cys Arg Thr Val Ala Phe Glu
 1 5 10 15
 Thr Gly Met Gln Asn Thr Gln Leu Cys Ser Thr Ile Val Gln Leu Ser
 20 25 30
 5 Phe Thr Pro Glu Glu
 35

(2) INFORMATION FOR SEQ ID NO:168:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 44 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:168:

Arg Glu Phe Ala Glu Arg Arg Leu Trp Gly Cys Asp Asp Leu Ser Trp
 1 5 10 15
 15 Arg Leu Asp Ala Glu Gly Cys Gly Pro Thr Pro Ser Asn Arg Ala Val
 20 25 30
 Lys His Arg Lys Pro Arg Pro Arg Ser Pro Ala Leu
 35 40

(2) INFORMATION FOR SEQ ID NO:169:

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 41 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:169:

Ser Gly Ser His Ser Gly Gly Met Asn Arg Ala Tyr Gly Asp Val Phe
 1 5 10 15
 25 Arg Glu Leu Arg Asp Arg Trp Tyr Ala Thr Ser His His Thr Arg Pro
 20 25 30
 Thr Pro Gln Leu Pro Arg Gly Pro Asn
 35 40

(2) INFORMATION FOR SEQ ID NO:170:

(i) SEQUENCE CHARACTERISTICS:

- 30 (A) LENGTH: 20 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:170:

35 Ser Thr Pro Pro Ser Arg Glu Ala Tyr Ser Arg Pro Tyr Ser Val Asp
 1 5 10 15
 Ser Asp Ser Asp
 20

(2) INFORMATION FOR SEQ ID NO:171:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

5

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:171:

Ser	Thr	Pro	Pro	Ser	Arg	Glu	Ala	Tyr	Ser	Arg	Pro	Tyr	Ser	Val	Asp
1				5				10						15	
Ser	Asp	Ser	Asp	Thr	Asn	Ala	Lys	His	Ser	Ser	His	Asn			
			20				25								

10

(2) INFORMATION FOR SEQ ID NO:172:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

15

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:172:

Thr	Asn	Ala	Lys	His	Ser	Ser	His	Asn	Arg	Arg	Leu	Arg	Thr	Arg	Ser
1				5				10						15	
Arg	Pro	Asn													

20

(2) INFORMATION FOR SEQ ID NO:173:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 9 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:173:

Thr	Asn	Ala	Lys	His	Ser	Ser	His	Asn
1				5				

(2) INFORMATION FOR SEQ ID NO:174:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

30

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:174:

Ser	Ser	His	Asn	Arg	Arg	Leu	Arg	Thr	Arg	Ser	Arg	Pro	Asn
1				5				10					

(2) INFORMATION FOR SEQ ID NO:175:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:175:

Arg Arg Leu Arg Thr Arg Ser Arg Pro Asn
 1 5 10

(2) INFORMATION FOR SEQ ID NO:176:

(i) SEQUENCE CHARACTERISTICS:

10

- (A) LENGTH: 708 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:176:

15 Met Gly Met Ser Lys Ser His Ser Phe Phe Gly Tyr Pro Leu Ser Ile
 1 5 10 15
 Phe Phe Ile Val Val Asn Glu Phe Cys Glu Arg Phe Ser Tyr Tyr Gly
 20 25 30
 Met Arg Ala Ile Leu Ile Leu Tyr Phe Thr Asn Phe Ile Ser Trp Asp
 35 40 45
 Asp Asn Leu Ser Thr Ala Ile Tyr His Thr Phe Val Ala Leu Cys Tyr
 50 55 60
 Leu Thr Pro Ile Leu Gly Ala Leu Ile Ala Asp Ser Trp Leu Gly Lys
 65 70 75 80
 20 Phe Lys Thr Ile Val Ser Leu Ser Ile Val Tyr Thr Ile Gly Gln Ala
 85 90 95
 Val Thr Ser Val Ser Ser Ile Asn Asp Leu Thr Asp His Asn His Asp
 100 105 110
 Gly Thr Pro Asp Ser Leu Pro Val His Val Val Leu Ser Leu Ile Gly
 115 120 125
 Leu Ala Leu Ile Ala Leu Gly Thr Gly Gly Ile Lys Pro Cys Val Ser
 130 135 140
 25 Ala Phe Gly Gly Asp Gln Phe Glu Glu Gly Gln Glu Lys Gln Arg Asn
 145 150 155 160
 Arg Phe Phe Ser Ile Phe Tyr Leu Ala Ile Asn Ala Gly Ser Leu Leu
 165 170 175
 Ser Thr Ile Ile Thr Pro Met Leu Arg Val Gln Gln Cys Gly Ile His
 180 185 190
 Ser Lys Gln Ala Cys Tyr Pro Leu Ala Phe Gly Val Pro Ala Ala Leu
 195 200 205
 Met Ala Val Ala Leu Ile Val Phe Val Leu Gly Ser Gly Met Tyr Lys
 210 215 220
 30 Lys Phe Lys Pro Gln Gly Asn Ile Met Gly Lys Val Ala Lys Cys Ile
 225 230 235 240
 Gly Phe Ala Ile Lys Asn Arg Phe Arg His Arg Ser Lys Ala Phe Pro
 245 250 255
 Lys Arg Glu His Trp Leu Asp Trp Ala Lys Glu Lys Tyr Asp Glu Arg
 260 265 270
 Leu Ile Ser Gln Ile Lys Met Val Thr Arg Val Met Phe Leu Tyr Ile
 275 280 285
 35 Pro Leu Pro Met Phe Trp Ala Leu Phe Asp Gln Gln Gly Ser Arg Trp
 290 295 300
 Thr Leu Gln Ala Thr Thr Met Ser Gly Lys Ile Gly Ala Leu Glu Ile
 305 310 315 320
 Gln Pro Asp Gln Met Gln Thr Val Asn Ala Ile Leu Ile Val Ile Met

				325					330					335
	Val	Pro	Ile	Phe	Asp	Ala	Val	Leu	Tyr	Pro	Leu	Ile	Ala	Lys
				340					345					350
	Phe	Asn	Phe	Thr	Ser	Leu	Lys	Lys	Met	Ala	Val	Gly	Met	Val
			355					360					365	
	Ser	Met	Ala	Phe	Val	Val	Ala	Ala	Ile	Val	Gln	Val	Glu	Ile
		370						375				380		
5	Thr	Leu	Pro	Val	Phe	Pro	Lys	Gly	Asn	Glu	Val	Gln	Ile	Lys
	385					390					395			400
	Asn	Ile	Gly	Asn	Asn	Thr	Met	Asn	Ile	Ser	Leu	Pro	Gly	Glu
				405						410				415
	Thr	Leu	Gly	Pro	Met	Ser	Gln	Thr	Asn	Ala	Phe	Met	Thr	Phe
			420						425					430
	Asn	Lys	Leu	Thr	Arg	Ile	Asn	Ile	Ser	Ser	Pro	Gly	Ser	Pro
		435						440					445	
10	Ala	Val	Thr	Asp	Asp	Phe	Lys	Gln	Gly	Gln	Arg	His	Thr	Leu
	450						455					460		
	Trp	Ala	Pro	Asn	His	Tyr	Gln	Val	Val	Lys	Asp	Gly	Leu	Asn
	465					470					475			480
	Pro	Glu	Lys	Gly	Glu	Asn	Gly	Ile	Arg	Phe	Val	Asn	Thr	Phe
				485						490				495
	Leu	Ile	Thr	Ile	Thr	Met	Ser	Gly	Lys	Val	Tyr	Ala	Asn	Ile
			500					505					510	
	Tyr	Asn	Ala	Ser	Thr	Tyr	Gln	Phe	Phe	Pro	Ser	Gly	Ile	Lys
		515						520					525	
15	Thr	Ile	Ser	Ser	Thr	Glu	Ile	Pro	Pro	Gln	Cys	Gln	Pro	Asn
	530						535					540		
	Thr	Phe	Tyr	Leu	Glu	Phe	Gly	Ser	Ala	Tyr	Thr	Tyr	Ile	Val
	545				550				555					560
	Lys	Asn	Asp	Ser	Cys	Pro	Glu	Val	Lys	Val	Phe	Glu	Asp	Ile
				565					570					575
	Asn	Thr	Val	Asn	Met	Ala	Leu	Gln	Ile	Pro	Gln	Tyr	Phe	Leu
			580					585					590	
20	Cys	Gly	Glu	Val	Val	Phe	Ser	Val	Thr	Gly	Leu	Glu	Phe	Ser
		595						600				605		
	Gln	Ala	Pro	Ser	Asn	Met	Lys	Ser	Val	Leu	Gln	Ala	Gly	Trp
		610					615					620		
	Thr	Val	Ala	Val	Gly	Asn	Ile	Ile	Val	Leu	Ile	Val	Ala	Gly
	625				630						635			640
	Gln	Phe	Ser	Lys	Gln	Trp	Ala	Glu	Tyr	Ile	Leu	Phe	Ala	Ala
				645					650					655
	Leu	Val	Val	Cys	Val	Val	Phe	Ala	Ile	Met	Ala	Arg	Phe	Tyr
			660					665					670	
25	Ile	Asn	Pro	Ala	Glu	Ile	Glu	Ala	Gln	Phe	Asp	Glu	Asp	Glu
		675						680				685		
	Asn	Arg	Leu	Glu	Lys	Ser	Asn	Pro	Tyr	Phe	Met	Ser	Gly	Ala
		690					695					700		
	Gln	Lys	Gln	Met										
	705													

(2) INFORMATION FOR SEQ ID NO:177:

- 30 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 3345 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (ix) FEATURE:
- 35 (A) NAME/KEY: Coding Sequence
 (B) LOCATION: 88...2583
 (D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:177:

	GAATTCCGTC	TCGACCACTG	AATGGAAGAA	AAGGACTTTT	AACCACCATT	TTGTGACTTA	60
	CAGAAAGGAA	TTTGAATAAA	GAAAACT	ATG ATA	CTT CAG	GCC CAT CTT CAC TCC	114
			Met	Ile	Leu	Gln Ala His Leu His Ser	
			1			5	
5	CTG TGT CTT CTT ATG CTT TAT TTG GCA ACT GGA TAT GGC CAA GAG GGG						162
	Leu Cys Leu Leu Met Leu Tyr Leu Ala Thr Gly Tyr Gly Gln Glu Gly						
	10		15		20	25	
	AAG TTT AGT GGA CCC CTG AAA CCC ATG ACA TTT TCT ATT TAT GAA GGC						210
	Lys Phe Ser Gly Pro Leu Lys Pro Met Thr Phe Ser Ile Tyr Glu Gly						
		30		35		40	
10	CAA GAA CCG AGT CAA ATT ATA TTC CAG TTT AAG GCC AAT CCT CCT GCT						258
	Gln Glu Pro Ser Gln Ile Ile Phe Gln Phe Lys Ala Asn Pro Pro Ala						
		45		50		55	
	GTG ACT TTT GAA CTA ACT GGG GAG ACA GAC AAC ATA TTT GTG ATA GAA						306
	Val Thr Phe Glu Leu Thr Gly Glu Thr Asp Asn Ile Phe Val Ile Glu						
		60		65		70	
	CGG GAG GGA CTT CTG TAT TAC AAC AGA GCC TTG GAC AGG GAA ACA AGA						354
	Arg Glu Gly Leu Leu Tyr Tyr Asn Arg Ala Leu Asp Arg Glu Thr Arg						
		75		80		85	
15	TCT ACT CAC AAT CTC CAG GTT GCA GCC CTG GAC GCT AAT GGA ATT ATA						402
	Ser Thr His Asn Leu Gln Val Ala Ala Leu Asp Ala Asn Gly Ile Ile						
		90		95		100	105
	GTG GAG GGT CCA GTC CCT ATC ACC ATA GAA GTG AAG GAC ATC AAC GAC						450
	Val Glu Gly Pro Val Pro Ile Thr Ile Glu Val Lys Asp Ile Asn Asp						
		110		115		120	
20	AAT CGA CCC ACG TTT CTC CAG TCA AAG TAC GAA GGC TCA GTA AGG CAG						498
	Asn Arg Pro Thr Phe Leu Gln Ser Lys Tyr Glu Gly Ser Val Arg Gln						
		125		130		135	
	AAC TCT CGC CCA GGA AAG CCC TTC TTG TAT GTC AAT GCC ACA GAC CTG						546
	Asn Ser Arg Pro Gly Lys Pro Phe Leu Tyr Val Asn Ala Thr Asp Leu						
		140		145		150	
25	GAT GAT CCG GCC ACT CCC AAT GGC CAG CTT TAT TAC CAG ATT GTC ATC						594
	Asp Asp Pro Ala Thr Pro Asn Gly Gln Leu Tyr Tyr Gln Ile Val Ile						
		155		160		165	
	CAG CTT CCC ATG ATC AAC AAT GTC ATG TAC TTT CAG ATC AAC AAC AAA						642
	Gln Leu Pro Met Ile Asn Asn Val Met Tyr Phe Gln Ile Asn Asn Lys						
		170		175		180	185
30	ACG GGA GCC ATC TCT CTT ACC CGA GAG GGA TCT CAG GAA TTG AAT CCT						690
	Thr Gly Ala Ile Ser Leu Thr Arg Glu Gly Ser Gln Glu Leu Asn Pro						
		190		195		200	
	GCT AAG AAT CCT TCC TAT AAT CTG GTG ATC TCA GTG AAG GAC ATG GGA						738
	Ala Lys Asn Pro Ser Tyr Asn Leu Val Ile Ser Val Lys Asp Met Gly						
		205		210		215	
	GGC CAG AGT GAG AAT TCC TTC AGT GAT ACC ACA TCT GTG GAT ATC ATA						786
	Gly Gln Ser Glu Asn Ser Phe Ser Asp Thr Thr Ser Val Asp Ile Ile						
		220		225		230	
35	GTG ACA GAG AAT ATT TGG AAA GCA CCA AAA CCT GTG GAG ATG GTG GAA						834
	Val Thr Glu Asn Ile Trp Lys Ala Pro Lys Pro Val Glu Met Val Glu						
		235		240		245	

	AAC	TCA	ACT	GAT	CCT	CAC	CCC	ATC	AAA	ATC	ACT	CAG	GTG	CGG	TGG	AAT	882
	Asn	Ser	Thr	Asp	Pro	His	Pro	Ile	Lys	Ile	Thr	Gln	Val	Arg	Trp	Asn	250
																	265
	GAT	CCC	GGT	GCA	CAA	TAT	TCC	TTA	GTT	GAC	AAA	GAG	AAG	CTG	CCA	AGA	930
	Asp	Pro	Gly	Ala	Gln	Tyr	Ser	Leu	Val	Asp	Lys	Glu	Lys	Leu	Pro	Arg	270
																	280
5	TTC	CCA	TTT	TCA	ATT	GAC	CAG	GAA	GGA	GAT	ATT	TAC	GTG	ACT	CAG	CCC	978
	Phe	Pro	Phe	Ser	Ile	Asp	Gln	Glu	Gly	Asp	Ile	Tyr	Val	Thr	Gln	Pro	285
																	290
	TTG	GAC	CGA	GAA	GAA	AAG	GAT	GCA	TAT	GTT	TTT	TAT	GCA	GTT	GCA	AAG	1026
	Leu	Asp	Arg	Glu	Glu	Lys	Asp	Ala	Tyr	Val	Phe	Tyr	Ala	Val	Ala	Lys	300
																	305
10	GAT	GAG	TAC	GGA	AAA	CCA	CTT	TCA	TAT	CCG	CTG	GAA	ATT	CAT	GTA	AAA	1074
	Asp	Glu	Tyr	Gly	Lys	Pro	Leu	Ser	Tyr	Pro	Leu	Glu	Ile	His	Val	Lys	315
																	320
	GTT	AAA	GAT	ATT	AAT	GAT	AAT	CCA	CCT	ACA	TGT	CCG	TCA	CCA	GTA	ACC	1122
	Val	Lys	Asp	Ile	Asn	Asp	Asn	Pro	Pro	Thr	Cys	Pro	Ser	Pro	Val	Thr	330
																	335
	GTA	TTT	GAG	GTC	CAG	GAG	AAT	GAA	CGA	CTG	GGT	AAC	AGT	ATC	GGG	ACC	1170
15	Val	Phe	Glu	Val	Gln	Glu	Asn	Glu	Arg	Leu	Gly	Asn	Ser	Ile	Gly	Thr	350
																	355
	CTT	ACT	GCA	CAT	GAC	AGG	GAT	GAA	GAA	AAT	ACT	GCC	AAC	AGT	TTT	CTA	1218
	Leu	Thr	Ala	His	Asp	Arg	Asp	Glu	Glu	Asn	Thr	Ala	Asn	Ser	Phe	Leu	365
																	370
	AAC	TAC	AGG	ATT	GTG	GAG	CAA	ACT	CCC	AAA	CTT	CCC	ATG	GAT	GGA	CTC	1266
20	Asn	Tyr	Arg	Ile	Val	Glu	Gln	Thr	Pro	Lys	Leu	Pro	Met	Asp	Gly	Leu	380
																	385
	TTC	CTA	ATC	CAA	ACC	TAT	GCT	GGA	ATG	TTA	CAG	TTA	GCT	AAA	CAG	TCC	1314
	Phe	Leu	Ile	Gln	Thr	Tyr	Ala	Gly	Met	Leu	Gln	Leu	Ala	Lys	Gln	Ser	395
																	400
	TTG	AAG	AAG	CAA	GAT	ACT	CCT	CAG	TAC	AAC	TTA	ACG	ATA	GAG	GTG	TCT	1362
	Leu	Lys	Lys	Gln	Asp	Thr	Pro	Gln	Tyr	Asn	Leu	Thr	Ile	Glu	Val	Ser	410
																	415
25	GAC	AAA	GAT	TTC	AAG	ACC	CTT	TGT	TTT	GTG	CAA	ATC	AAC	GTT	ATT	GAT	1410
	Asp	Lys	Asp	Phe	Lys	Thr	Leu	Cys	Phe	Val	Gln	Ile	Asn	Val	Ile	Asp	430
																	435
	ATC	AAT	GAT	CAG	ATC	CCC	ATC	TTT	GAA	AAA	TCA	GAT	TAT	GGA	AAC	CTG	1458
	Ile	Asn	Asp	Gln	Ile	Pro	Ile	Phe	Glu	Lys	Ser	Asp	Tyr	Gly	Asn	Leu	445
																	450
30	ACT	CTT	GCT	GAA	GAC	ACA	AAC	ATT	GGG	TCC	ACC	ATC	TTA	ACC	ATC	CAG	1506
	Thr	Leu	Ala	Glu	Asp	Thr	Asn	Ile	Gly	Ser	Thr	Ile	Leu	Thr	Ile	Gln	460
																	465
	GCC	ACT	GAT	GCT	GAT	GAG	CCA	TTT	ACT	GGG	AGT	TCT	AAA	ATT	CTG	TAT	1554
	Ala	Thr	Asp	Ala	Asp	Glu	Pro	Phe	Thr	Gly	Ser	Ser	Lys	Ile	Leu	Tyr	475
																	480
	CAT	ATC	ATA	AAG	GGA	GAC	AGT	GAG	GGA	CGC	CTG	GGG	GTT	GAC	ACA	GAT	1602
35	His	Ile	Ile	Lys	Gly	Asp	Ser	Glu	Gly	Arg	Leu	Gly	Val	Asp	Thr	Asp	490
																	495
	CCC	CAT	ACC	AAC	ACC	GGA	TAT	GTC	ATA	ATT	AAA	AAG	CCT	CTT	GAT	TTT	1650
	Pro	His	Thr	Asn	Thr	Gly	Tyr	Val	Ile	Ile	Lys	Lys	Pro	Leu	Asp	Phe	500
																	505

						510																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																
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	CAC CAG ACT GGG ATA CCC ACT GTG GGC ATG GCA GTT GGT ATA CTG CTG	2466
	His Gln Thr Gly Ile Pro Thr Val Gly Met Ala Val Gly Ile Leu Leu	
	780 785 790	
	ACC ACC CTT CTG GTG ATT GGT ATA ATT TTA GCA GTT GTG TTT ATC CGC	2514
	Thr Thr Leu Leu Val Ile Gly Ile Ile Leu Ala Val Val Phe Ile Arg	
	795 800 805	
5	ATA AAG AAG GAT AAA GGC AAA GAT AAT GTT GAA AGT GCT CAA GCA TCT	2562
	Ile Lys Lys Asp Lys Gly Lys Asp Asn Val Glu Ser Ala Gln Ala Ser	
	810 815 820 825	
	GAA GTC AAA CCT CTG AGA AGC TGAATTTGAA AAGGAATGTT TGAATTTATA TAGC	2617
	Glu Val Lys Pro Leu Arg Ser	
	830	
10	AAGTGCTATT TCAGCAACAA CCATCTCATC CTATTACTTT TCATCTAACG TGCATTATAA	2677
	TTTTTTTAAAC AGATATTCCC TCTTGTCCTT TAATATTTGC TAAATATTTT TTTTTTGAGG	2737
	TGGAGTCTTG CTCTGTCGCC CAGGCTGGAG TACAGTGGTG TGATCCCAGC TCACTGCAAC	2797
	CTCCGCCTCC TGGGTTTACA TGATTCTCCT GCCTCAGCTT CCTAAGTAGC TGGGTTTACA	2857
	GGCACCACACC ACCATGCCCA GCTAATTTT GTATTTTAA TAGAGACGGG GTTTCGCCAT	2917
	TTGGCCAGGC TGGTCTTGAA CTCCTGACGT CAAGTGATCT GCCTGCCTTG GTCTCCCAAT	2977
	ACAGGCATGA ACCACTGCAC CCACCTACTT AGATATTTCA TGTGCTATAG ACATTAGAGA	3037
	GATTTTTTCAT TTTTCCATGA CATTTTTCCT CTCTGCAAAT GGCTTAGCTA CTTGTGTTTT	3097
	TCCCTTTTGG GGCAAGACAG ACTCATTTAA TATTCTGTAC ATTTTTCCTT TATCAAGGAG	3157
15	ATATATCAGT GTTGTCTCAT AGAACTGCCT GGATTCCATT TATGTTTTTT CTGATTCCAT	3217
	CCTGTGTCCC CTTCATCCTT GACTCCTTTG GTATTTCACT GAATTTCAAA CATTGTTCAG	3277
	AGAAGAAAAA AGTGAGGACT CAGGAAAAAT AAATAAATAA AAGAACAGCC TTTTGCGGCC	3337
	GCGAATTC	3345

(2) INFORMATION FOR SEQ ID NO:178:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 832 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:178:

25	Met Ile Leu Gln Ala His Leu His Ser Leu Cys Leu Leu Met Leu Tyr	
	1 5 10 15	
	Leu Ala Thr Gly Tyr Gly Gln Glu Gly Lys Phe Ser Gly Pro Leu Lys	
	20 25 30	
	Pro Met Thr Phe Ser Ile Tyr Glu Gly Gln Glu Pro Ser Gln Ile Ile	
	35 40 45	
	Phe Gln Phe Lys Ala Asn Pro Pro Ala Val Thr Phe Glu Leu Thr Gly	
	50 55 60	
	Glu Thr Asp Asn Ile Phe Val Ile Glu Arg Glu Gly Leu Leu Tyr Tyr	
	65 70 75 80	
30	Asn Arg Ala Leu Asp Arg Glu Thr Arg Ser Thr His Asn Leu Gln Val	
	85 90 95	
	Ala Ala Leu Asp Ala Asn Gly Ile Ile Val Glu Gly Pro Val Pro Ile	
	100 105 110	
	Thr Ile Glu Val Lys Asp Ile Asn Asp Asn Arg Pro Thr Phe Leu Gln	
	115 120 125	
	Ser Lys Tyr Glu Gly Ser Val Arg Gln Asn Ser Arg Pro Gly Lys Pro	
	130 135 140	
35	Phe Leu Tyr Val Asn Ala Thr Asp Leu Asp Asp Pro Ala Thr Pro Asn	
	145 150 155 160	
	Gly Gln Leu Tyr Tyr Gln Ile Val Ile Gln Leu Pro Met Ile Asn Asn	
	165 170 175	
	Val Met Tyr Phe Gln Ile Asn Asn Lys Thr Gly Ala Ile Ser Leu Thr	
	180 185 190	

	Arg	Glu	Gly	Ser	Gln	Glu	Leu	Asn	Pro	Ala	Lys	Asn	Pro	Ser	Tyr	Asn
		195						200					205			
	Leu	Val	Ile	Ser	Val	Lys	Asp	Met	Gly	Gly	Gln	Ser	Glu	Asn	Ser	Phe
	210						215					220				
	Ser	Asp	Thr	Thr	Ser	Val	Asp	Ile	Ile	Val	Thr	Glu	Asn	Ile	Trp	Lys
	225					230					235					240
	Ala	Pro	Lys	Pro	Val	Glu	Met	Val	Glu	Asn	Ser	Thr	Asp	Pro	His	Pro
					245					250					255	
5	Ile	Lys	Ile	Thr	Gln	Val	Arg	Trp	Asn	Asp	Pro	Gly	Ala	Gln	Tyr	Ser
				260					265					270		
	Leu	Val	Asp	Lys	Glu	Lys	Leu	Pro	Arg	Phe	Pro	Phe	Ser	Ile	Asp	Gln
			275					280					285			
	Glu	Gly	Asp	Ile	Tyr	Val	Thr	Gln	Pro	Leu	Asp	Arg	Glu	Glu	Lys	Asp
	290						295					300				
	Ala	Tyr	Val	Phe	Tyr	Ala	Val	Ala	Lys	Asp	Glu	Tyr	Gly	Lys	Pro	Leu
	305					310					315					320
10	Ser	Tyr	Pro	Leu	Glu	Ile	His	Val	Lys	Val	Lys	Asp	Ile	Asn	Asp	Asn
					325					330					335	
	Pro	Pro	Thr	Cys	Pro	Ser	Pro	Val	Thr	Val	Phe	Glu	Val	Gln	Glu	Asn
				340					345					350		
	Glu	Arg	Leu	Gly	Asn	Ser	Ile	Gly	Thr	Leu	Thr	Ala	His	Asp	Arg	Asp
			355					360					365			
	Glu	Glu	Asn	Thr	Ala	Asn	Ser	Phe	Leu	Asn	Tyr	Arg	Ile	Val	Glu	Gln
	370					375						380				
	Thr	Pro	Lys	Leu	Pro	Met	Asp	Gly	Leu	Phe	Leu	Ile	Gln	Thr	Tyr	Ala
	385					390						395				400
15	Gly	Met	Leu	Gln	Leu	Ala	Lys	Gln	Ser	Leu	Lys	Lys	Gln	Asp	Thr	Pro
					405					410					415	
	Gln	Tyr	Asn	Leu	Thr	Ile	Glu	Val	Ser	Asp	Lys	Asp	Phe	Lys	Thr	Leu
				420					425					430		
	Cys	Phe	Val	Gln	Ile	Asn	Val	Ile	Asp	Ile	Asn	Asp	Gln	Ile	Pro	Ile
			435					440					445			
	Phe	Glu	Lys	Ser	Asp	Tyr	Gly	Asn	Leu	Thr	Leu	Ala	Glu	Asp	Thr	Asn
	450						455					460				
20	Ile	Gly	Ser	Thr	Ile	Leu	Thr	Ile	Gln	Ala	Thr	Asp	Ala	Asp	Glu	Pro
	465					470					475					480
	Phe	Thr	Gly	Ser	Ser	Lys	Ile	Leu	Tyr	His	Ile	Ile	Lys	Gly	Asp	Ser
				485						490					495	
	Glu	Gly	Arg	Leu	Gly	Val	Asp	Thr	Asp	Pro	His	Thr	Asn	Thr	Gly	Tyr
				500					505					510		
	Val	Ile	Ile	Lys	Lys	Pro	Leu	Asp	Phe	Glu	Thr	Ala	Ala	Val	Ser	Asn
			515					520					525			
	Ile	Val	Phe	Lys	Ala	Glu	Asn	Pro	Glu	Pro	Leu	Val	Phe	Gly	Val	Lys
	530						535					540				
25	Tyr	Asn	Ala	Ser	Ser	Phe	Ala	Lys	Phe	Thr	Leu	Ile	Val	Thr	Asp	Val
	545					550					555					560
	Asn	Glu	Ala	Pro	Gln	Phe	Ser	Gln	His	Val	Phe	Gln	Ala	Lys	Val	Ser
					565					570					575	
	Glu	Asp	Val	Ala	Ile	Gly	Thr	Lys	Val	Gly	Asn	Val	Thr	Ala	Lys	Asp
				580					585					590		
	Pro	Glu	Gly	Leu	Asp	Ile	Ser	Tyr	Ser	Leu	Arg	Gly	Asp	Thr	Arg	Gly
			595					600					605			
30	Trp	Leu	Lys	Ile	Asp	His	Val	Thr	Gly	Glu	Ile	Phe	Ser	Val	Ala	Pro
	610						615					620				
	Leu	Asp	Arg	Glu	Ala	Gly	Ser	Pro	Tyr	Arg	Val	Gln	Val	Val	Ala	Thr
	625					630					635					640
	Glu	Val	Gly	Gly	Ser	Leu	Ser	Ser	Val	Ser	Glu	Phe	His	Leu	Ile	
				645						650				655		
	Leu	Met	Asp	Val	Asn	Asp	Asn	Pro	Pro	Arg	Leu	Ala	Lys	Asp	Tyr	Thr
				660					665					670		
	Gly	Leu	Phe	Phe	Cys	His	Pro	Leu	Ser	Ala	Pro	Gly	Ser	Leu	Ile	Phe
			675					680					685			
35	Glu	Ala	Thr	Asp	Asp	Asp	Gln	His	Leu	Phe	Arg	Gly	Pro	His	Phe	Thr
	690						695					700				
	Phe	Ser	Leu	Gly	Ser	Gly	Ser	Leu	Gln	Asn	Asp	Trp	Glu	Val	Ser	Lys
	705					710					715					720

(2) INFORMATION FOR SEO ID NO:179:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1827 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:179:

- 186 -

	305				310				315				320
	Leu	Asp	Phe	Tyr	Ile	Leu	Leu	Gly	Asp	Thr	Pro	Glu	Gln
					325	Leu	Val	Gly	Leu	Pro	Ala	Met	Pro
	Gln	Tyr	Gln	Gln	Leu	Val	Gly	Leu	Pro	Ala	Met	Pro	Ala
					340	Leu	Ser	Arg	Trp	Asn	Tyr	Lys	Ser
	Leu	Gly	Phe	Gln	Leu	Ser	Arg	Trp	Asn	Tyr	Lys	Ser	Leu
					355	Val	Val	Arg	Arg	Asn	Arg	Glu	Ala
5	Lys	Glu	Val	Val	Arg	Arg	Asn	Arg	Glu	Ala	Gly	Ile	Pro
	Gln	Val	Thr	Asp	Ile	Asp	Tyr	Met	Glu	Asp	Lys	Lys	Asp
	Asp	Gln	Val	Ala	Phe	Asn	Gly	Leu	Pro	Gln	Phe	Val	Gln
					405	Leu	Val	Ile	Ile	Leu	Asp	Pro	Ala
	Asp	His	Gly	Gln	Lys	Tyr	Val	Ile	Ile	Leu	Asp	Pro	Ala
					420	Gly	Thr	Thr	Thr	Ala	Thr	Tyr	Glu
10	Gly	Arg	Arg	Ala	Asn	Gly	Thr	Thr	Thr	Ala	Thr	Tyr	Glu
	Thr	Gln	His	Val	Trp	Ile	Asn	Glu	Ser	Asp	Gly	Ser	Thr
	Gly	Glu	Val	Trp	Pro	Gly	Leu	Thr	Val	Tyr	Pro	Asp	Phe
	Asn	Cys	Ile	Asp	Trp	Ala	Asn	Glu	Cys	Ser	Ile	Phe	His
	Val	Gln	Tyr	Asp	Gly	Leu	Trp	Ile	Asp	Met	Asn	Glu	Val
15	Ile	Gln	Gly	Ser	Thr	Lys	Gly	Cys	Asn	Val	Asn	Lys	Leu
	Pro	Phe	Thr	Pro	Asp	Ile	Leu	Asp	Lys	Leu	Met	Tyr	Ser
	Cys	Met	Asp	Ala	Val	Gln	Asn	Trp	Gly	Lys	Gln	Tyr	Asp
	Leu	Tyr	Gly	Tyr	Ser	Met	Ala	Ile	Ala	Thr	Glu	Gln	Ala
20	Val	Phe	Pro	Asn	Lys	Arg	Ser	Phe	Ile	Leu	Thr	Arg	Ser
	Gly	Ser	Gly	Arg	His	Ala	Ala	His	Trp	Leu	Gly	Asp	Asn
	Trp	Glu	Gln	Met	Glu	Trp	Ser	Ile	Thr	Gly	Met	Leu	Glu
	Phe	Gly	Ile	Pro	Leu	Val	Gly	Ala	Asp	Ile	Cys	Gly	Phe
	Thr	Thr	Glu	Glu	Leu	Cys	Arg	Arg	Trp	Met	Gln	Leu	Gly
25	Pro	Phe	Ser	Arg	Asn	His	Asn	Ser	Asp	Gly	Tyr	Glu	His
	Ala	Phe	Phe	Gly	Gln	Asn	Ser	Leu	Leu	Val	Lys	Ser	Ser
	Leu	Thr	Ile	Arg	Tyr	Thr	Leu	Leu	Pro	Phe	Leu	Tyr	Thr
	Lys	Ala	His	Val	Phe	Gly	Glu	Thr	Val	Ala	Arg	Pro	Val
30	Phe	Tyr	Glu	Asp	Thr	Asn	Ser	Trp	Ile	Glu	Asp	Thr	Glu
	Gly	Pro	Ala	Leu	Leu	Ile	Thr	Pro	Val	Leu	Lys	Gln	Gly
	Val	Ser	Ala	Tyr	Ile	Pro	Asp	Ala	Ile	Trp	Tyr	Asp	Tyr
	Ala	Lys	Arg	Pro	Trp	Arg	Lys	Gln	Arg	Val	Asp	Met	Tyr
	Asp	Lys	Ile	Gly	Leu	His	Leu	Arg	Gly	Gly	Tyr	Ile	Ile
35	Glu	Pro	Asp	Val	Thr	Thr	Ala	Ser	Arg	Lys	Asn	Pro	Leu
	Ile	Val	Ala	Leu	Gly	Glu	Asn	Asn	Thr	Ala	Lys	Gly	Asp
	Asp	Asp	Gly	Glu	Thr	Lys	Asp	Thr	Ile	Gln	Asn	Gly	Asn

			835				840				845								
	Tyr	Thr	Phe	Ser	Val	Ser	Asn	Asn	Thr	Leu	Asp	Ile	Val	Cys	Thr	His			
		850					855					860							
	Ser	Ser	Tyr	Gln	Glu	Gly	Thr	Thr	Leu	Ala	Phe	Gln	Thr	Val	Lys	Ile			
	865					870					875					880			
	Leu	Gly	Leu	Thr	Asp	Ser	Val	Thr	Glu	Val	Arg	Val	Ala	Glu	Asn	Asn			
					885					890					895				
5	Gln	Pro	Met	Asn	Ala	His	Ser	Asn	Phe	Thr	Tyr	Asp	Ala	Ser	Asn	Gln			
				900					905					910					
	Val	Leu	Leu	Ile	Ala	Asp	Leu	Lys	Leu	Asn	Leu	Gly	Arg	Asn	Phe	Ser			
		915						920					925						
	Val	Gln	Trp	Asn	Gln	Ile	Phe	Ser	Glu	Asn	Glu	Arg	Phe	Asn	Cys	Tyr			
		930					935					940							
	Pro	Asp	Ala	Asp	Leu	Ala	Thr	Glu	Gln	Lys	Cys	Thr	Gln	Arg	Gly	Cys			
	945				950						955					960			
	Val	Trp	Arg	Thr	Gly	Ser	Ser	Leu	Ser	Lys	Ala	Pro	Glu	Cys	Tyr	Phe			
10				965						970					975				
	Pro	Arg	Gln	Asp	Asn	Ser	Tyr	Ser	Val	Asn	Ser	Ala	Arg	Tyr	Ser	Ser			
				980					985					990					
	Met	Gly	Ile	Thr	Ala	Asp	Leu	Gln	Leu	Asn	Thr	Ala	Asn	Ala	Arg	Ile			
		995					1000						1005						
	Lys	Leu	Pro	Ser	Asp	Pro	Ile	Ser	Thr	Leu	Arg	Val	Glu	Val	Lys	Tyr			
	1010					1015					1020								
	His	Lys	Asn	Asp	Met	Leu	Gln	Phe	Lys	Ile	Tyr	Asp	Pro	Gln	Lys	Lys			
	025				1030					1035					1040				
15	Arg	Tyr	Glu	Val	Pro	Leu	Asn	Ile	Pro	Thr	Thr	Pro	Ile	Ser					
				1045				1050					1055						
	Thr	Tyr	Glu	Asp	Arg	Leu	Tyr	Asp	Val	Glu	Ile	Lys	Glu	Asn	Pro	Phe			
			1060					1065					1070						
	Gly	Ile	Gln	Ile	Arg	Arg	Arg	Ser	Gly	Arg	Val	Ile	Trp	Asp	Ser				
		1075					1080					1085							
	Trp	Leu	Pro	Gly	Phe	Ala	Phe	Asn	Asp	Gln	Phe	Ile	Gln	Ile	Ser	Thr			
	1090					1095					1100								
	Arg	Leu	Pro	Ser	Glu	Tyr	Ile	Tyr	Gly	Phe	Gly	Glu	Val	Glu	His	Thr			
20	105				1110					1115					1120				
	Ala	Phe	Lys	Arg	Asp	Leu	Asn	Trp	Asn	Thr	Trp	Gly	Met	Phe	Thr	Arg			
				1125					1130					1135					
	Asp	Gln	Pro	Pro	Gly	Tyr	Lys	Leu	Asn	Ser	Tyr	Gly	Phe	His	Pro	Tyr			
			1140					1145					1150						
	Tyr	Met	Ala	Leu	Glu	Glu	Glu	Gly	Asn	Ala	His	Gly	Val	Phe	Leu	Leu			
		1155					1160					1165							
	Asn	Ser	Asn	Ala	Met	Asp	Val	Thr	Phe	Gln	Pro	Thr	Pro	Ala	Leu	Thr			
		1170				1175					1180								
25	Tyr	Arg	Thr	Val	Gly	Gly	Ile	Leu	Asp	Phe	Tyr	Met	Phe	Leu	Gly	Pro			
	185				1190					1195					1200				
	Thr	Pro	Gln	Val	Ala	Thr	Lys	Gln	Tyr	His	Glu	Val	Ile	Gly	His	Pro			
				1205				1210						1215					
	Val	Met	Pro	Ala	Tyr	Trp	Ala	Leu	Gly	Phe	Gln	Leu	Cys	Arg	Tyr	Gly			
			1220					1225					1230						
	Tyr	Ala	Asn	Thr	Ser	Glu	Val	Arg	Glu	Leu	Tyr	Asp	Ala	Met	Val	Ala			
		1235						1240				1245							
	Ala	Asn	Ile	Pro	Tyr	Asp	Val	Gln	Tyr	Thr	Asp	Ile	Asp	Tyr	Met	Glu			
30		1250				1255					1260								
	Arg	Gln	Leu	Asp	Phe	Thr	Ile	Gly	Glu	Ala	Phe	Gln	Asp	Leu	Pro	Gln			
	265				1270					1275					1280				
	Phe	Val	Asp	Lys	Ile	Arg	Gly	Glu	Gly	Met	Arg	Tyr	Ile	Ile	Ile	Leu			
				1285					1290					1295					
	Asp	Pro	Ala	Ile	Ser	Gly	Asn	Glu	Thr	Lys	Thr	Tyr	Pro	Ala	Phe	Glu			
			1300					1305					1310						
	Arg	Gly	Gln	Gln	Asn	Asp	Val	Phe	Val	Lys	Trp	Pro	Asn	Thr	Asn	Asp			
		1315					1320					1325							
35	Ile	Cys	Trp	Ala	Lys	Val	Trp	Pro	Asp	Leu	Pro	Asn	Ile	Thr	Ile	Asp			
		1330				1335					1340								
	Lys	Thr	Leu	Thr	Glu	Asp	Glu	Ala	Val	Asn	Ala	Ser	Arg	Ala	His	Val			
	345				1350					1355					1360				
	Ala	Phe	Pro	Asp	Phe	Phe	Arg	Thr	Ser	Thr	Ala	Glu	Trp	Trp	Ala	Arg			

1365 1370 1375
 Glu Ile Val Asp Phe Tyr Asn Glu Lys Met Lys Phe Asp Gly Leu Trp
 1380 1385 1390
 Ile Asp Met Asn Glu Pro Ser Ser Phe Val Asn Gly Thr Thr Thr Asn
 1395 1400 1405
 Gln Cys Arg Asn Asp Glu Leu Asn Tyr Pro Pro Tyr Phe Pro Glu Leu
 1410 1415 1420
 5 Thr Lys Arg Thr Asp Gly Leu His Phe Arg Thr Ile Cys Met Glu Ala
 425 1430 1435 1440
 Glu Gln Ile Leu Ser Asp Gly Thr Ser Val Leu His Tyr Asp Val His
 1445 1450 1455
 Asn Leu Tyr Gly Trp Ser Gln Met Lys Pro Thr His Asp Ala Leu Gln
 1460 1465 1470
 Lys Thr Thr Gly Lys Arg Gly Ile Val Ile Ser Arg Ser Thr Tyr Pro
 1475 1480 1485
 Thr Ser Gly Arg Trp Gly Gly His Trp Leu Gly Asp Asn Tyr Ala Arg
 1490 1495 1500
 10 Trp Asp Asn Met Asp Lys Ser Ile Ile Gly Met Met Glu Phe Ser Leu
 505 1510 1515 1520
 Phe Gly Ile Ser Tyr Thr Gly Ala Asp Ile Cys Gly Phe Phe Asn Asn
 1525 1530 1535
 Ser Glu Tyr His Leu Cys Thr Arg Trp Met Gln Leu Gly Ala Phe Tyr
 1540 1545 1550
 Pro Tyr Ser Arg Asn His Asn Ile Ala Asn Thr Arg Arg Gln Asp Pro
 1555 1560 1565
 15 Ala Ser Trp Asn Glu Thr Phe Ala Glu Met Ser Arg Asn Ile Leu Asn
 1570 1575 1580
 Ile Arg Tyr Thr Leu Leu Pro Tyr Phe Tyr Thr Gln Met His Glu Ile
 585 1590 1595 1600
 His Ala Asn Gly Gly Thr Val Ile Arg Pro Leu Leu His Glu Phe Phe
 1605 1610 1615
 Asp Glu Lys Pro Thr Trp Asp Ile Phe Lys Gln Phe Leu Trp Gly Pro
 1620 1625 1630
 Ala Phe Met Val Thr Pro Val Leu Glu Pro Tyr Val Gln Thr Val Asn
 1635 1640 1645
 20 Ala Tyr Val Pro Asn Ala Arg Trp Phe Asp Tyr His Thr Gly Lys Asp
 1650 1655 1660
 Ile Gly Val Arg Gly Gln Phe Gln Thr Phe Asn Ala Ser Tyr Asp Thr
 665 1670 1675 1680
 Ile Asn Leu His Val Arg Gly Gly His Ile Leu Pro Cys Gln Glu Pro
 1685 1690 1695
 Ala Gln Asn Thr Phe Tyr Ser Arg Gln Lys His Met Lys Leu Ile Val
 1700 1705 1710
 25 Ala Ala Asp Asp Asn Gln Met Ala Gln Gly Ser Leu Phe Trp Asp Asp
 1715 1720 1725
 Gly Glu Ser Ile Asp Thr Tyr Glu Arg Asp Leu Tyr Leu Ser Val Gln
 1730 1735 1740
 Phe Asn Leu Asn Gln Thr Thr Leu Thr Ser Thr Ile Leu Lys Arg Gly
 745 1750 1755 1760
 Tyr Ile Asn Lys Ser Glu Thr Arg Leu Gly Ser Leu His Val Trp Gly
 1765 1770 1775
 Lys Gly Thr Thr Pro Val Asn Ala Val Thr Leu Thr Tyr Asn Gly Asn
 1780 1785 1790
 30 Lys Asn Ser Leu Pro Phe Asn Glu Asp Thr Thr Asn Met Ile Leu Arg
 1795 1800 1805
 Ile Asp Leu Thr Thr His Asn Val Thr Leu Glu Glu Pro Ile Glu Ile
 1810 1815 1820
 Asn Trp Ser
 825

(2) INFORMATION FOR SEQ ID NO:180:

35

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 2284 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION: 45...2099

(D) OTHER INFORMATION:

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:180:

	GCCTTACTGC AGGAAGGCAC TCCGAAGACA TAAGTCGGTG AGAC ATG GCT GAA GAT	56
	Met Ala Glu Asp	
	1	
10	AAA AGC AAG AGA GAC TCC ATC GAG ATG AGT ATG AAG GGA TGC CAG ACA	104
	Lys Ser Lys Arg Asp Ser Ile Glu Met Ser Met Lys Gly Cys Gln Thr	
	5 10 15 20	
	AAC AAC GGG TTT GTC CAT AAT GAA GAC ATT CTG GAG CAG ACC CCG GAT	152
	Asn Asn Gly Phe Val His Asn Glu Asp Ile Leu Glu Gln Thr Pro Asp	
	25 30 35	
15	CCA GGC AGC TCA ACA GAC AAC CTG AAG CAC AGC ACC AGG GGC ATC CTT	200
	Pro Gly Ser Ser Thr Asp Asn Leu Lys His Ser Thr Arg Gly Ile Leu	
	40 45 50	
	GGC TCC CAG GAG CCC GAC TTC AAG GGC GTC CAG CCC TAT GCG GGG ATG	248
	Gly Ser Gln Glu Pro Asp Phe Lys Gly Val Gln Pro Tyr Ala Gly Met	
	55 60 65	
20	CCC AAG GAG GTG CTG TTC CAG TTC TCT GGC CAG GCC CGC TAC CGC ATA	296
	Pro Lys Glu Val Leu Phe Gln Phe Ser Gly Gln Ala Arg Tyr Arg Ile	
	70 75 80	
	CCT CGG GAG ATC CTC TTC TGG CTC ACA GTG GCT TCT GTG CTG GTG CTC	344
	Pro Arg Glu Ile Leu Trp Leu Thr Val Ala Ser Val Leu Val Leu	
	85 90 95 100	
	ATC GCG GCC ACC ATA GCC ATC ATT GCC CTC TCT CCA AAG TGC CTA GAC	392
	Ile Ala Ala Thr Ile Ala Ile Ile Ala Leu Ser Pro Lys Cys Leu Asp	
	105 110 115	
25	TGG TGG CAG GAG GGG CCC ATG TAC CAG ATC TAC CCA AGG TCT TTC AAG	440
	Trp Trp Gln Glu Gly Pro Met Tyr Gln Ile Tyr Pro Arg Ser Phe Lys	
	120 125 130	
	GAC AGT AAC AAG GAT GGG AAC GGA GAT CTG AAA GGT ATT CAA GAT AAA	488
	Asp Ser Asn Lys Asp Gly Asn Gly Asp Leu Lys Gly Ile Gln Asp Lys	
	135 140 145	
30	CTG GAC TAC ATC ACA GCT TTA AAT ATA AAA ACT GTT TGG ATT ACT TCA	536
	Leu Asp Tyr Ile Thr Ala Leu Asn Ile Lys Thr Val Trp Ile Thr Ser	
	150 155 160	
	TTT TAT AAA TCG TCC CTT AAA GAT TTC AGA TAT GGT GTT GAA GAT TTC	584
	Phe Tyr Lys Ser Ser Leu Lys Asp Phe Arg Tyr Gly Val Glu Asp Phe	
	165 170 175 180	
35	CGG GAA GTT GAT CCC ATT TTT GGA ACG ATG GAA GAT TTT GAG AAT CTG	632
	Arg Glu Val Asp Pro Ile Phe Gly Thr Met Glu Asp Phe Glu Asn Leu	
	185 190 195	
	GTT GCA GCC ATA CAT GAT AAA GGT TTA AAA TTA ATC ATC GAT TTC ATA	680
	Val Ala Ala Ile His Asp Lys Gly Leu Lys Leu Ile Ile Asp Phe Ile	

	200						205						210						
	CCA Pro	AAC Asn	CAC His 215	ACG Thr	AGT Ser	GAT Asp	AAA Lys	CAT His 220	ATT Ile	TGG Trp	TTT Phe	CAA Gln	TTG Leu 225	AGT Ser	CGG Arg	ACA Thr	728		
5	CGG Arg	ACA Thr 230	GGA Gly	AAA Lys	TAT Tyr	ACT Thr	GAT Asp 235	TAT Tyr	TAT Tyr	ATC Ile	TGG Trp	CAT His 240	GAC Asp	TGT Cys	ACC Thr	CAT His	776		
	GAA Glu 245	AAT Asn	GGC Gly	AAA Lys	ACC Thr	ATT Ile 250	CCA Pro	CCC Pro	AAC Asn	AAC Asn	TGG Trp 255	TTA Leu	AGT Ser	GTG Val	TAT Tyr	GGA Gly 260	824		
10	AAC Asn	TCC Ser	AGT Ser	TGG Trp	CAC His 265	TTT Phe	GAC Asp	GAA Glu	GTG Val	CGA Arg 270	AAC Asn	CAA Gln	TGT Cys	TAT Tyr	TTT Phe 275	CAT His	872		
	CAG Gln	TTT Phe	ATG Met	AAA Lys 280	GAG Glu	CAA Gln	CCT Pro	GAT Asp	TTA Leu 285	AAT Asn	TTC Phe	CGC Arg	AAT Asn	CCT Pro 290	GAT Asp	GTT Val	920		
	CAA Gln	GAA Glu	GAA Glu 295	ATA Ile	AAA Lys	GAA Glu	ATT Ile	TTA Leu 300	CGG Arg	TTC Phe	TGG Trp	CTC Leu	ACA Thr 305	AAG Lys	GGT Gly	GTT Val	968		
15	GAT Asp	GGT Gly 310	TTT Phe	AGT Ser	TTG Leu	GAT Asp	GCT Ala 315	GTT Val	AAA Lys	TTC Phe	CTC Leu	CTA Leu 320	GAA Glu	GCA Ala	AAG Lys	CAC His	1016		
	CTG Leu 325	AGA Arg	GAT Asp	GAG Glu	ATC Ile	CAA Gln 330	GTA Val	AAT Asn	AAG Lys	ACC Thr	CAA Gln 335	ATC Ile	CCG Pro	GAC Asp	ACG Thr	GTC Val 340	1064		
20	ACA Thr	CAA Gln	TAC Tyr	TCG Ser	GAG Glu 345	CTG Leu	TAC Tyr	CAT His	GAC Asp	TTC Phe 350	ACC Thr	ACC Thr	ACG Thr	CAG Gln	GTG Val 355	GGA Gly	1112		
	ATG Met	CAC His	GAC Asp	ATT Ile 360	GTC Val	CGC Arg	AGC Ser	TTC Phe	CGG Arg 365	CAG Gln	ACC Thr	ATG Met	GAC Asp	CAA Gln 370	TAC Tyr	AGC Ser	1160		
25	ACG Thr	GAG Glu	CCC Pro 375	GGC Gly	AGA Arg	TAC Tyr	AGG Arg	TTC Phe 380	ATG Met	GGG Gly	ACT Thr	GAA Glu	GCC Ala 385	TAT Tyr	GCA Ala	GAG Glu	1208		
	AGT Ser	ATT Ile 390	GAC Asp	AGG Arg	ACC Thr	GTG Val	ATG Met 395	TAC Tyr	TAT Tyr	GGA Gly	TTG Leu	CCA Pro 400	TTT Phe	ATC Ile	CAA Gln	GAA Glu	1256		
30	GCT Ala 405	GAT Asp	TTT Phe	CCC Pro	TTC Phe	AAC Asn 410	AAT Asn	TAC Tyr	CTC Leu	AGC Ser	ATG Met 415	CTA Leu	GAC Asp	ACT Thr	GTT Val	TCT Ser 420	1304		
	GGG Gly	AAC Asn	AGC Ser	GTG Val 425	TAT Tyr	GAG Glu	GTT Val	ATC Ile	ACA Thr	TCC Ser 430	TGG Trp	ATG Met	GAA Glu	AAC Asn	ATG Met 435	CCA Pro	1352		
	GAA Glu	GGA Gly	AAA Lys 440	TGG Trp	CCT Pro	AAC Asn	TGG Trp	ATG Met	ATT Ile 445	GGT Gly	GGA Gly	CCA Pro	GAC Asp	AGT Ser 450	TCA Ser	CGG Arg	1400		
35	CTG Leu	ACT Thr	TCG Ser 455	CGT Arg	TTG Leu	GGG Gly	AAT Asn	CAG Gln 460	TAT Tyr	GTC Val	AAC Asn	GTG Val	ATG Met 465	AAC Asn	ATG Met	CTT Leu	1448		

	CTT TTC ACA CTC CCT GGA ACT CCT ATA ACT TAC TAT GGA GAA GAA ATT	1496
	Leu Phe Thr Leu Pro Gly Thr Pro Ile Thr Tyr Tyr Gly Glu Glu Ile	
	470 475 480	
	GGA ATG GGA AAT ATT GTA GCC GCA AAT CTC AAT GAA AGC TAT GAT ATT	1544
	Gly Met Gly Asn Ile Val Ala Ala Asn Leu Asn Glu Ser Tyr Asp Ile	
	485 490 495 500	
5	AAT ACC CTT CGC TCA AAG TCA CCA ATG CAG TGG GAC AAT AGT TCA AAT	1592
	Asn Thr Leu Arg Ser Lys Ser Pro Met Gln Trp Asp Asn Ser Ser Asn	
	505 510 515	
	GCT GGT TTT TCT GAA GCT AGT AAC ACC TGG TTA CCT ACC AAT TCA GAT	1640
	Ala Gly Phe Ser Glu Ala Ser Asn Thr Trp Leu Pro Thr Asn Ser Asp	
	520 525 530	
10	TAC CAC ACT GTG AAT GTT GAT GTC CAA AAG ACT CAG CCC AGA TCG GCT	1688
	Tyr His Thr Val Asn Val Asp Val Gln Lys Thr Gln Pro Arg Ser Ala	
	535 540 545	
	TTG AAG TTA TAT CAA GAT TTA AGT CTA CTT CAT GCC AAT GAG CTA CTC	1736
	Leu Lys Leu Tyr Gln Asp Leu Ser Leu Leu His Ala Asn Glu Leu Leu	
	550 555 560	
15	CTC AAC AGG GGC TGG TTT TGC CAT TTG AGG AAT GAC AGC CAC TAT GTT	1784
	Leu Asn Arg Gly Trp Phe Cys His Leu Arg Asn Asp Ser His Tyr Val	
	565 570 575 580	
	GTG TAC ACA AGA GAG CTG GAT GGC ATC GAC AGA ATC TTT ATC GTG GTT	1832
	Val Tyr Thr Arg Glu Leu Asp Gly Ile Asp Arg Ile Phe Ile Val Val	
	585 590 595	
	CTG AAT TTT GGA GAA TCA ACA CTG TTA AAT CTA CAT AAT ATG ATT TCG	1880
	Leu Asn Phe Gly Glu Ser Thr Leu Leu Asn Leu His Asn Met Ile Ser	
20	600 605 610	
	GGC CTT CCC GCT AAA ATA AGA ATA AGG TTA AGT ACC AAT TCT GCC GAC	1928
	Gly Leu Pro Ala Lys Ile Arg Ile Arg Leu Ser Thr Asn Ser Ala Asp	
	615 620 625	
	AAA GGC AGT AAA GTT GAT ACA AGT GGC ATT TTT CTG GAC AAG GGA GAG	1976
	Lys Gly Ser Lys Val Asp Thr Ser Gly Ile Phe Leu Asp Lys Gly Glu	
	630 635 640	
25	GGA CTC ATC TTT GAA CAC AAC ACG AAG AAT CTC CTT CAT CGC CAA ACA	2024
	Gly Leu Ile Phe Glu His Asn Thr Lys Asn Leu Leu His Arg Gln Thr	
	645 650 655 660	
	GCT TTC AGA GAT AGA TGC TTT GTT TCC AAT CGA GCA TGC TAT TCC AGT	2072
	Ala Phe Arg Asp Arg Cys Phe Val Ser Asn Arg Ala Cys Tyr Ser Ser	
	665 670 675	
30	GTA CTG AAC ATA CTG TAT ACC TCG TGT TAGGCACCTT TATGAAGAGA TGAAGAC	2126
	Val Leu Asn Ile Leu Tyr Thr Ser Cys	
	680 685	
	ACTGGCATT CAGTGGGATT GTAAGCATTT GTAATAGCTT CATGTACAGC ATGCTGCTTG	2186
	GTGAACAATC ATTAATTCTT CGATATTTCT GTAGCTTGAA TGTAACCGCT TTAAGAAAGG	2246
	TTCTCAAATG TTTTGAAAAA AATAAAATGT TTAAAAGT	2284

(2) INFORMATION FOR SEQ ID NO:181:

35

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 685 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:181:

	Met	Ala	Glu	Asp	Lys	Ser	Lys	Arg	Asp	Ser	Ile	Glu	Met	Ser	Met	Lys
5	1				5					10					15	
	Gly	Cys	Gln	Thr	Asn	Asn	Gly	Phe	Val	His	Asn	Glu	Asp	Ile	Leu	Glu
				20					25					30		
	Gln	Thr	Pro	Asp	Pro	Gly	Ser	Ser	Thr	Asp	Asn	Leu	Lys	His	Ser	Thr
			35					40					45			
	Arg	Gly	Ile	Leu	Gly	Ser	Gln	Glu	Pro	Asp	Phe	Lys	Gly	Val	Gln	Pro
		50				55						60				
	Tyr	Ala	Gly	Met	Pro	Lys	Glu	Val	Leu	Phe	Gln	Phe	Ser	Gly	Gln	Ala
	65					70					75					80
10	Arg	Tyr	Arg	Ile	Pro	Arg	Glu	Ile	Leu	Phe	Trp	Leu	Thr	Val	Ala	Ser
				85						90					95	
	Val	Leu	Val	Leu	Ile	Ala	Ala	Thr	Ile	Ala	Ile	Ile	Ala	Leu	Ser	Pro
				100					105					110		
	Lys	Cys	Leu	Asp	Trp	Trp	Gln	Glu	Gly	Pro	Met	Tyr	Gln	Ile	Tyr	Pro
			115					120					125			
	Arg	Ser	Phe	Lys	Asp	Ser	Asn	Lys	Asp	Gly	Asn	Gly	Asp	Leu	Lys	Gly
		130					135					140				
15	Ile	Gln	Asp	Lys	Leu	Asp	Tyr	Ile	Thr	Ala	Leu	Asn	Ile	Lys	Thr	Val
	145					150					155					160
	Trp	Ile	Thr	Ser	Phe	Tyr	Lys	Ser	Ser	Leu	Lys	Asp	Phe	Arg	Tyr	Gly
				165						170					175	
	Val	Glu	Asp	Phe	Arg	Glu	Val	Asp	Pro	Ile	Phe	Gly	Thr	Met	Glu	Asp
				180					185					190		
	Phe	Glu	Asn	Leu	Val	Ala	Ala	Ile	His	Asp	Lys	Gly	Leu	Lys	Leu	Ile
			195					200					205			
	Ile	Asp	Phe	Ile	Pro	Asn	His	Thr	Ser	Asp	Lys	His	Ile	Trp	Phe	Gln
		210					215					220				
20	Leu	Ser	Arg	Thr	Arg	Thr	Gly	Lys	Tyr	Thr	Asp	Tyr	Tyr	Ile	Trp	His
						230					235					240
	Asp	Cys	Thr	His	Glu	Asn	Gly	Lys	Thr	Ile	Pro	Pro	Asn	Asn	Trp	Leu
				245							250				255	
	Ser	Val	Tyr	Gly	Asn	Ser	Ser	Trp	His	Phe	Asp	Glu	Val	Arg	Asn	Gln
				260					265					270		
	Cys	Tyr	Phe	His	Gln	Phe	Met	Lys	Glu	Gln	Pro	Asp	Leu	Asn	Phe	Arg
			275					280					285			
25	Asn	Pro	Asp	Val	Gln	Glu	Glu	Ile	Lys	Glu	Ile	Leu	Arg	Phe	Trp	Leu
							295					300				
	Thr	Lys	Gly	Val	Asp	Gly	Phe	Ser	Leu	Asp	Ala	Val	Lys	Phe	Leu	Leu
		305				310					315					320
	Glu	Ala	Lys	His	Leu	Arg	Asp	Glu	Ile	Gln	Val	Asn	Lys	Thr	Gln	Ile
				325						330					335	
	Pro	Asp	Thr	Val	Thr	Gln	Tyr	Ser	Glu	Leu	Tyr	His	Asp	Phe	Thr	Thr
				340					345					350		
	Thr	Gln	Val	Gly	Met	His	Asp	Ile	Val	Arg	Ser	Phe	Arg	Gln	Thr	Met
			355					360					365			
30	Asp	Gln	Tyr	Ser	Thr	Glu	Pro	Gly	Arg	Tyr	Arg	Phe	Met	Gly	Thr	Glu
							375					380				
	Ala	Tyr	Ala	Glu	Ser	Ile	Asp	Arg	Thr	Val	Met	Tyr	Tyr	Gly	Leu	Pro
						390					395					400
	Phe	Ile	Gln	Glu	Ala	Asp	Phe	Pro	Phe	Asn	Asn	Tyr	Leu	Ser	Met	Leu
					405						410				415	
	Asp	Thr	Val	Ser	Gly	Asn	Ser	Val	Tyr	Glu	Val	Ile	Thr	Ser	Trp	Met
				420					425					430		
35	Glu	Asn	Met	Pro	Glu	Gly	Lys	Trp	Pro	Asn	Trp	Met	Ile	Gly	Gly	Pro
			435					440					445			
	Asp	Ser	Ser	Arg	Leu	Thr	Ser	Arg	Leu	Gly	Asn	Gln	Tyr	Val	Asn	Val
		450						455				460				
	Met	Asn	Met	Leu	Leu	Phe	Thr	Leu	Pro	Gly	Thr	Pro	Ile	Thr	Tyr	Tyr
						470					475					480

5	Gly	Glu	Glu	Ile	Gly	Met	Gly	Asn	Ile	Val	Ala	Ala	Asn	Leu	Asn	Glu
					485					490					495	
	Ser	Tyr	Asp	Ile	Asn	Thr	Leu	Arg	Ser	Lys	Ser	Pro	Met	Gln	Trp	Asp
				500					505					510		
	Asn	Ser	Ser	Asn	Ala	Gly	Phe	Ser	Glu	Ala	Ser	Asn	Thr	Trp	Leu	Pro
			515				520					525				
	Thr	Asn	Ser	Asp	Tyr	His	Thr	Val	Asn	Val	Asp	Val	Gln	Lys	Thr	Gln
							535					540				
	Pro	Arg	Ser	Ala	Leu	Lys	Leu	Tyr	Gln	Asp	Leu	Ser	Leu	Leu	His	Ala
						550					555					560
	Asn	Glu	Leu	Leu	Leu	Asn	Arg	Gly	Trp	Phe	Cys	His	Leu	Arg	Asn	Asp
						565				570					575	
	Ser	His	Tyr	Val	Val	Tyr	Thr	Arg	Glu	Leu	Asp	Gly	Ile	Asp	Arg	Ile
									585					590		
	Phe	Ile	Val	Val	Leu	Asn	Phe	Gly	Glu	Ser	Thr	Leu	Leu	Asn	Leu	His
								600					605			
10	Asn	Met	Ile	Ser	Gly	Leu	Pro	Ala	Lys	Ile	Arg	Ile	Arg	Leu	Ser	Thr
							615					620				
	Asn	Ser	Ala	Asp	Lys	Gly	Ser	Lys	Val	Asp	Thr	Ser	Gly	Ile	Phe	Leu
						630				635					640	
	Asp	Lys	Gly	Glu	Gly	Leu	Ile	Phe	Glu	His	Asn	Thr	Lys	Asn	Leu	Leu
						645				650					655	
	His	Arg	Gln	Thr	Ala	Phe	Arg	Asp	Arg	Cys	Phe	Val	Ser	Asn	Arg	Ala
						660			665					670		
15	Cys	Tyr	Ser	Ser	Val	Leu	Asn	Ile	Leu	Tyr	Thr	Ser	Cys			
								680					685			

(2) INFORMATION FOR SEQ ID NO:182:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 54 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:182:

[illegible]

(2) INFORMATION FOR SEQ ID NO:183:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:183:

35 Ser Ala Arg Asp Ser Gly Pro Ala Glu Asp Gly Ser Arg Ala Val Arg
 1 5 10 15
 Leu Asn Gly

(2) INFORMATION FOR SEQ ID NO:184:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 21 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: peptide
- 5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:184:
- Asp Gly Ser Arg Ala Val Arg Leu Asn Gly Val Glu Asn Ala Asn Thr
 1 5 10 15
 Arg Lys Ser Ser Arg
 20
- (2) INFORMATION FOR SEQ ID NO:185:
- 10 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 19 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: peptide
- 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:185:
- Glu Asn Ala Asn Thr Arg Lys Ser Ser Arg Ser Asn Pro Arg Gly Arg
 1 5 10 15
 Arg His Pro
- (2) INFORMATION FOR SEQ ID NO:186:
- 20 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 11 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:186:
- 25 Thr Arg Lys Ser Ser Arg Ser Asn Pro Arg Gly
 1 5 10
- (2) INFORMATION FOR SEQ ID NO:187:
- 30 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 21 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:187:
- Ser Arg Pro Tyr Ser Val Asp Ser Asp Ser Asp Thr Asn Ala Lys His
 1 5 10 15
 35 Ser Ser His Asn Arg
 20
- (2) INFORMATION FOR SEQ ID NO:188:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:188:

Thr Asn Ala Lys His Ser Ser His Asn Arg Arg Leu Arg Thr Arg Ser
 1 5 10 15
 Arg Pro Asn

(2) INFORMATION FOR SEQ ID NO:189:

10

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:189:

Arg Tyr Lys His Asp Ile Gly Cys Asp Ala Gly Val Asp Lys Lys Ser
 1 5 10 15
 Ser Ser Val Arg Gly Gly Cys Gly
 20

(2) INFORMATION FOR SEQ ID NO:190:

20

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 26 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:190:

25

Gly Cys Asp Ala Gly Val Asp Lys Lys Ser Ser Ser Val Arg Gly Gly
 1 5 10 15
 Cys Gly Ala His Ser Ser Pro Pro Arg Ala
 20 25

(2) INFORMATION FOR SEQ ID NO:191:

30

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:191:

Gly Ala His Ser Ser Pro Pro Arg Ala Gly Arg Gly Pro Arg Gly Thr
 1 5 10 15
 Met Val Ser Arg Leu
 20

(2) INFORMATION FOR SEQ ID NO:192:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

5

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:192:

Glu Asn Ala Asn Thr Arg Lys Ser Ser Arg
 1 5 10

(2) INFORMATION FOR SEQ ID NO:193:

10

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:193:

Lys Lys Arg Ile Ala Gly Leu Pro Trp Tyr Arg Cys Arg Thr Val Ala
 1 5 10 15
 Phe Glu Thr Gly Met Gln Asn Thr Gln Leu Cys Ser Thr Ile Val Gln
 20 25 30
 Leu Ser Phe Thr Pro Glu Glu
 35

20

(2) INFORMATION FOR SEQ ID NO:194:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:194:

Arg Lys Ser Ser Arg Ser Asn Pro Arg Gly
 1 5 10

(2) INFORMATION FOR SEQ ID NO:195:

(i) SEQUENCE CHARACTERISTICS:

30

- (A) LENGTH: 9 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:195:

35 Ser Asn Pro Arg Gly Arg Arg His Pro
 1 5

(2) INFORMATION FOR SEQ ID NO:196:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 9 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: peptide
- 5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:196:
- Thr Asn Ala Lys His Ser Ser His Asn
 1 5
- (2) INFORMATION FOR SEQ ID NO:197:
- 10 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 10 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:197:
- 15 Ser Ser His Asn Arg Arg Leu Arg Thr Arg
 1 5 10
- (2) INFORMATION FOR SEQ ID NO:198:
- 20 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 10 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:198:
- Arg Arg Leu Arg Thr Arg Ser Arg Pro Asn
 1 5 10
- 25 (2) INFORMATION FOR SEQ ID NO:199:
- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 19 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: peptide
- 30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:199:
- Arg Val Gly Gln Cys Thr Asp Ser Asp Val Arg Arg Pro Trp Ala Arg
 1 5 10 15
 Ser Cys Ala
- 35 (2) INFORMATION FOR SEQ ID NO:200:
- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 21 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:200:

5 Val Arg Arg Pro Trp Ala Arg Ser Cys Ala His Gln Gly Cys Gly Ala
 1 5 10 15
 Gly Thr Arg Asn Ser
 20

(2) INFORMATION FOR SEQ ID NO:201:

(i) SEQUENCE CHARACTERISTICS:

10 (A) LENGTH: 19 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:201:

15 Gly Thr Arg Asn Ser His Gly Cys Ile Thr Arg Pro Leu Arg Gln Ala
 1 5 10 15
 Ser Gln His

(2) INFORMATION FOR SEQ ID NO:202:

(i) SEQUENCE CHARACTERISTICS:

20 (A) LENGTH: 40 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:202:

25 Ser Thr Pro Pro Ser Arg Glu Ala Tyr Ser Arg Pro Tyr Ser Val Asp
 1 5 10 15
 Ser Asp Ser Asp Thr Met Ala Lys His Ser Ser His Asn Arg Arg Leu
 20 25 30
 Arg Thr Arg Ser Arg Pro Asn Gly
 35 40

(2) INFORMATION FOR SEQ ID NO:203:

(i) SEQUENCE CHARACTERISTICS:

30 (A) LENGTH: 4 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:203:

35 Tyr Ser Lys Val
 1

(2) INFORMATION FOR SEQ ID NO:204:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 4 amino acids

- (B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:204:
- 5 Phe Pro His Leu
1
- (2) INFORMATION FOR SEQ ID NO:205:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown
- 10 (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:205:
- Tyr Arg Gly Val
1
- 15 (2) INFORMATION FOR SEQ ID NO:206:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown
- 20 (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:206:
- Tyr Gln Thr Ile
1
- (2) INFORMATION FOR SEQ ID NO:207:
- 25 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:207:
- 30 Thr Glu Gln Phe
1
- (2) INFORMATION FOR SEQ ID NO:208:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown
- 35 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:208:

Thr Glu Val Met
1

(2) INFORMATION FOR SEQ ID NO:209:

- 5 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 4 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:209:

10 Thr Ser Ala Phe
1

(2) INFORMATION FOR SEQ ID NO:210:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 4 amino acids
 (B) TYPE: amino acid
 15 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:210:

Tyr Thr Arg Phe
1

20 (2) INFORMATION FOR SEQ ID NO:211:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 717 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

- 25 (ii) MOLECULE TYPE: DNA
 (ix) FEATURE:

- (A) NAME/KEY: Coding Sequence
 (B) LOCATION: 1...714
 (D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:211:

30 ATG TCC CCT ATA CTA GGT TAT TGG AAA ATT AAG GGC CTT GTG CAA CCC 48
 Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1 5 10 15

ACT CGA CTT CTT TTG GAA TAT CTT GAA GAA AAA TAT GAA GAG CAT TTG 96
 Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
 20 25 30

35 TAT GAG CGC GAT GAA GGT GAT AAA TGG CGA AAC AAA AAG TTT GAA TTG 144
 Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
 35 40 45

GGT TTG GAG TTT CCC AAT CTT CCT TAT TAT ATT GAT GGT GAT GTT AAA 192

	Gly	Leu	Glu	Phe	Pro	Asn	Leu	Pro	Tyr	Tyr	Ile	Asp	Gly	Asp	Val	Lys	
	50						55					60					
	TTA	ACA	CAG	TCT	ATG	GCC	ATC	ATA	CGT	TAT	ATA	GCT	GAC	AAG	CAC	AAC	240
	Leu	Thr	Gln	Ser	Met	Ala	Ile	Ile	Arg	Tyr	Ile	Ala	Asp	Lys	His	Asn	
	65					70				75						80	
5	ATG	TTG	GGT	GGT	TGT	CCA	AAA	GAG	CGT	GCA	GAG	ATT	TCA	ATG	CTT	GAA	288
	Met	Leu	Gly	Gly	Cys	Pro	Lys	Glu	Arg	Ala	Glu	Ile	Ser	Met	Leu	Glu	
					85				90						95		
	GGA	GCG	GTT	TTG	GAT	ATT	AGA	TAC	GGT	GTT	TCG	AGA	ATT	GCA	TAT	AGT	336
	Gly	Ala	Val	Leu	Asp	Ile	Arg	Tyr	Gly	Val	Ser	Arg	Ile	Ala	Tyr	Ser	
				100					105					110			
10	AAA	GAC	TTT	GAA	ACT	CTC	AAA	GTT	GAT	TTT	CTT	AGC	AAG	CTA	CCT	GAA	384
	Lys	Asp	Phe	Glu	Thr	Leu	Lys	Val	Asp	Phe	Leu	Ser	Lys	Leu	Pro	Glu	
			115					120					125				
	ATG	CTG	AAA	ATG	TTC	GAA	GAT	CGT	TTA	TGT	CAT	AAA	ACA	TAT	TTA	AAT	432
	Met	Leu	Lys	Met	Phe	Glu	Asp	Arg	Leu	Cys	His	Lys	Thr	Tyr	Leu	Asn	
		130					135					140					
	GGT	GAT	CAT	GTA	ACC	CAT	CCT	GAC	TTC	ATG	TTG	TAT	GAC	GCT	CTT	GAT	480
15	Gly	Asp	His	Val	Thr	His	Pro	Asp	Phe	Met	Leu	Tyr	Asp	Ala	Leu	Asp	
	145					150				155					160		
	GTT	GTT	TTA	TAC	ATG	GAC	CCA	ATG	TGC	CTG	GAT	GCG	TTC	CCA	AAA	TTA	528
	Val	Val	Leu	Tyr	Met	Asp	Pro	Met	Cys	Leu	Asp	Ala	Phe	Pro	Lys	Leu	
					165					170					175		
	GTT	TGT	TTT	AAA	AAA	CGT	ATT	GAA	GCT	ATC	CCA	CAA	ATT	GAT	AAG	TAC	576
	Val	Cys	Phe	Lys	Lys	Arg	Ile	Glu	Ala	Ile	Pro	Gln	Ile	Asp	Lys	Tyr	
				180				185						190			
20	TTG	AAA	TCC	AGC	AAG	TAT	ATA	GCA	TGG	CCT	TTG	CAG	GGC	TGG	CAA	GCC	624
	Leu	Lys	Ser	Ser	Lys	Tyr	Ile	Ala	Trp	Pro	Leu	Gln	Gly	Trp	Gln	Ala	
			195					200					205				
	ACG	TTT	GGT	GGT	GGC	GAC	CAT	CCT	CCA	AAA	TCG	GAT	CTG	GTT	CCG	CGT	672
	Thr	Phe	Gly	Gly	Gly	Asp	His	Pro	Pro	Lys	Ser	Asp	Leu	Val	Pro	Arg	
		210					215					220					
25	GGA	TCC	CCA	GGA	ATT	CCC	GGG	TCG	ACT	CGA	GCG	GCC	GCA	TCG	TGA		717
	Gly	Ser	Pro	Gly	Ile	Pro	Gly	Ser	Thr	Arg	Ala	Ala	Ala	Ser			
	225					230					235						

(2) INFORMATION FOR SEQ ID NO:212:

(i) SEQUENCE CHARACTERISTICS:

- 30 (A) LENGTH: 238 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:212:

35	Met	Ser	Pro	Ile	Leu	Gly	Tyr	Trp	Lys	Ile	Lys	Gly	Leu	Val	Gln	Pro	
	1				5				10						15		
	Thr	Arg	Leu	Leu	Glu	Tyr	Leu	Glu	Lys	Tyr	Glu	Glu	His	Leu			
				20				25					30				
	Tyr	Glu	Arg	Asp	Glu	Gly	Asp	Lys	Trp	Arg	Asn	Lys	Lys	Phe	Glu	Leu	
			35				40						45				

Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
 50 55 60
 Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
 65 70 75 80
 Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
 85 90 95
 Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
 100 105 110
 5 Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
 115 120 125
 Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
 130 135 140
 Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
 145 150 155 160
 Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
 165 170 175
 10 Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
 180 185 190
 Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
 195 200 205
 Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
 210 215 220
 Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser
 225 230 235

15 (2) INFORMATION FOR SEQ ID NO:213:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 282 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:213:

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1 5 10 15
 Thr Arg Leu Leu Glu Tyr Leu Glu Lys Tyr Glu Glu His Leu
 20 25 30
 Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
 35 40 45
 25 Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
 50 55 60
 Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
 65 70 75 80
 Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
 85 90 95
 Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
 100 105 110
 Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
 115 120 125
 30 Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
 130 135 140
 Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
 145 150 155 160
 Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
 165 170 175
 Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
 180 185 190
 35 Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
 195 200 205
 Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
 210 215 220
 Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser Gln

225		230		235		240									
Gly	Ser	Lys	Gln	Cys	Met	Gln	Tyr	Arg	Thr	Gly	Arg	Leu	Thr	Val	Gly
			245						250					255	
Ser	Glu	Tyr	Gly	Cys	Gly	Met	Asn	Pro	Ala	Arg	His	Ala	Thr	Pro	Ala
			260					265					270		
Tyr	Pro	Ala	Arg	Leu	Leu	Pro	Arg	Tyr	Arg						
		275					280								

5

(2) INFORMATION FOR SEQ ID NO:214:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 282 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

10

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:214:

	Met	Ser	Pro	Ile	Leu	Gly	Tyr	Trp	Lys	Ile	Lys	Gly	Leu	Val	Gln	Pro
	1				5					10					15	
	Thr	Arg	Leu	Leu	Leu	Glu	Tyr	Leu	Glu	Glu	Lys	Tyr	Glu	Glu	His	Leu
				20					25					30		
15	Tyr	Glu	Arg	Asp	Glu	Gly	Asp	Lys	Trp	Arg	Asn	Lys	Lys	Phe	Glu	Leu
		35					40					45				
	Gly	Leu	Glu	Phe	Pro	Asn	Leu	Pro	Tyr	Tyr	Ile	Asp	Gly	Asp	Val	Lys
		50				55					60					
	Leu	Thr	Gln	Ser	Met	Ala	Ile	Ile	Arg	Tyr	Ile	Ala	Asp	Lys	His	Asn
		65			70					75					80	
	Met	Leu	Gly	Gly	Cys	Pro	Lys	Glu	Arg	Ala	Glu	Ile	Ser	Met	Leu	Glu
				85					90					95		
	Gly	Ala	Val	Leu	Asp	Ile	Arg	Tyr	Gly	Val	Ser	Arg	Ile	Ala	Tyr	Ser
			100					105						110		
20	Lys	Asp	Phe	Glu	Thr	Leu	Lys	Val	Asp	Phe	Leu	Ser	Lys	Leu	Pro	Glu
		115					120						125			
	Met	Leu	Lys	Met	Phe	Glu	Asp	Arg	Leu	Cys	His	Lys	Thr	Tyr	Leu	Asn
		130					135					140				
	Gly	Asp	His	Val	Thr	His	Pro	Asp	Phe	Met	Leu	Tyr	Asp	Ala	Leu	Asp
		145				150					155				160	
	Val	Val	Leu	Tyr	Met	Asp	Pro	Met	Cys	Leu	Asp	Ala	Phe	Pro	Lys	Leu
				165					170					175		
	Val	Cys	Phe	Lys	Arg	Ile	Glu	Ala	Ile	Pro	Gln	Ile	Asp	Lys	Tyr	
25			180					185					190			
	Leu	Lys	Ser	Ser	Lys	Tyr	Ile	Ala	Trp	Pro	Leu	Gln	Gly	Trp	Gln	Ala
		195					200						205			
	Thr	Phe	Gly	Gly	Gly	Asp	His	Pro	Pro	Lys	Ser	Asp	Leu	Val	Pro	Arg
		210				215						220				
	Gly	Ser	Pro	Gly	Ile	Pro	Gly	Ser	Thr	Arg	Ala	Ala	Ala	Ser	Ser	Asp
		225			230					235					240	
	His	Ala	Leu	Gly	Thr	Asn	Leu	Arg	Ser	Asp	Asn	Ala	Lys	Glu	Pro	Gly
				245					250					255		
30	Asp	Tyr	Asn	Cys	Gly	Asn	Gly	Asn	Ser	Thr	Gly	Arg	Lys	Val	Phe	
			260			265							270			
	Asn	Arg	Arg	Arg	Pro	Ser	Ala	Ile	Pro	Thr						
		275					280									

(2) INFORMATION FOR SEQ ID NO:215:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 279 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

35

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:215:

```

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1      5      10      15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
      20      25      30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
 5      35      40      45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
      50      55      60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65      70      75      80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
      85      90      95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
      100      105      110
10 Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
      115      120      125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
      130      135      140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145      150      155      160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
      165      170      175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
15      180      185      190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
      195      200      205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
      210      215      220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser Pro
225      230      235      240
Cys Gly Gly Ser Trp Gly Arg Phe Met Gln Gly Gly Leu Phe Gly Gly
      245      250      255
20 Arg Thr Asp Gly Cys Gly Ala His Arg Asn Arg Thr Ser Ala Ser Leu
      260      265      270
Glu Pro Pro Ser Ser Asp Tyr
      275

```

(2) INFORMATION FOR SEQ ID NO:216:

(i) SEQUENCE CHARACTERISTICS:

25

- (A) LENGTH: 277 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:216:

```

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
30 1      5      10      15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
      20      25      30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
      35      40      45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
      50      55      60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65      70      75      80
35 Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
      85      90      95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
      100      105      110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu

```

```

      115      120      125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130      135      140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145      150      155      160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
165      170      175
5 Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180      185      190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
195      200      205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
210      215      220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Arg Gly
225      230      235      240
Ser Thr Gly Thr Ala Gly Gly Glu Arg Ser Gly Val Leu Asn Leu His
245      250      255
10 Thr Arg Asp Asn Ala Ser Gly Ser Gly Phe Lys Pro Trp Tyr Pro Ser
260      265      270
Asn Arg Gly His Lys
275

```

(2) INFORMATION FOR SEQ ID NO:217:

- (i) SEQUENCE CHARACTERISTICS:
- 15 (A) LENGTH: 277 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:217:

```

20 Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1 5 10 15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
20 25 30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
35 40 45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
50 55 60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65 70 75 80
25 Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
85 90 95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
100 105 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115 120 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130 135 140
30 Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145 150 155 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
165 170 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180 185 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
195 200 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
210 215 220
35 Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser His
225 230 235 240
Ser Gly Gly Met Asn Arg Ala Tyr Gly Asp Val Phe Arg Glu Leu Arg
245 250 255

```

Asp Arg Trp Asn Ala Thr Ser His His Thr Arg Pro Thr Pro Gln Leu
260 265 270
Pro Arg Gly Pro Asn
275

(2) INFORMATION FOR SEO ID NO:218:

5

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 248 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:218:

10

Met 1	Ser	Pro	Ile	Leu 5	Gly	Tyr	Trp	Lys	Ile 10	Lys	Gly	Leu	Val	Gln 15	Pro
Thr	Arg	Leu	Leu 20	Leu	Glu	Tyr	Leu	Glu 25	Glu	Lys	Tyr	Glu	Glu 30	His	Leu
Tyr	Glu	Arg 35	Asp	Glu	Gly	Asp	Lys 40	Trp	Arg	Asn	Lys	Lys 45	Phe	Glu	Leu
Gly	Leu	Glu	Phe	Pro	Asn	Leu 55	Pro	Tyr	Tyr	Ile	Asp 60	Gly	Asp	Val	Lys
Leu 65	Thr	Gln	Ser	Met	Ala 70	Ile	Ile	Arg	Tyr	Ile 75	Ala	Asp	Lys	His	Asn 80
Met	Leu	Gly	Gly	Cys 85	Pro	Lys	Glu	Arg	Ala 90	Glu	Ile	Ser	Met	Leu 95	Glu
Gly	Ala	Val	Leu 100	Asp	Ile	Arg	Tyr	Gly 105	Val	Ser	Arg	Ile	Ala 110	Tyr	Ser
Lys	Asp	Phe	Glu	Thr	Leu	Lys	Val 120	Asp	Phe	Leu	Ser	Lys 125	Leu	Pro	Glu
Met	Leu 130	Lys	Met	Phe	Glu	Asp 135	Arg	Leu	Cys	His 140	Lys	Thr	Tyr	Leu	Asn
Gly 145	Asp	His	Val	Thr	His 150	Pro	Asp	Phe	Met	Leu 155	Tyr	Asp	Ala	Leu 160	Asp
Val	Val	Leu	Tyr	Met 165	Asp	Pro	Met	Cys	Leu 170	Asp	Ala	Phe	Pro	Lys 175	Leu
Val	Cys	Phe	Lys 180	Lys	Arg	Ile	Glu	Ala 185	Ile	Pro	Gln	Ile	Asp 190	Lys	Tyr
Leu	Lys	Ser	Ser	Lys	Tyr	Ile	Ala 200	Trp	Pro	Leu	Gln	Gly 205	Trp	Gln	Ala
Thr	Phe 210	Gly	Gly	Gly	Asp	His 215	Pro	Pro	Lys	Ser	Asp 220	Leu	Val	Pro	Arg
Gly 225	Ser	Pro	Gly	Ile	Pro 230	Gly	Ser	Thr	Arg	Ala 235	Ala	Ala	Ser	Ser	His 240
Ser	Gly	Gly	Met	Asn 245	Arg	Ala	Tyr								

(2) INFORMATION FOR SEO ID NO:219:

30

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 248 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:219:

35

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1 5 10 15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
20 25 30

Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
 35 40 45
 Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
 50 55 60
 Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
 65 70 75 80
 Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
 85 90 95
 5 Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
 100 105 110
 Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
 115 120 125
 Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
 130 135 140
 Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
 145 150 155 160
 10 Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
 165 170 175
 Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
 180 185 190
 Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
 195 200 205
 Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
 210 215 220
 Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ser Gly Asp
 225 230 235 240
 15 Val Phe Arg Glu Leu Arg Asp Arg
 245

(2) INFORMATION FOR SEQ ID NO:220:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 248 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:220:

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1 5 10 15
 25 Thr Arg Leu Leu Glu Tyr Leu Glu Lys Tyr Glu Glu His Leu
 20 25 30
 Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
 35 40 45
 Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
 50 55 60
 Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
 65 70 75 80
 Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
 85 90 95
 30 Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
 100 105 110
 Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
 115 120 125
 Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
 130 135 140
 Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
 145 150 155 160
 35 Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
 165 170 175
 Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
 180 185 190
 Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala

```

      195      200      205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
      210      215      220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Trp Asn
225      230      235      240
Ala Thr Ser His His Thr Arg Pro
      245

```

5

(2) INFORMATION FOR SEQ ID NO:221:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 247 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

10

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:221:

```

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1      5      10      15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
      20      25      30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
15      35      40      45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
      50      55      60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65      70      75      80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
      85      90      95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
      100      105      110
20 Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
      115      120      125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
      130      135      140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145      150      155      160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
      165      170      175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
25      180      185      190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
      195      200      205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
      210      215      220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Thr Pro
225      230      235      240
Gln Leu Pro Arg Gly Pro Asn
      245

```

30

(2) INFORMATION FOR SEQ ID NO:222:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 258 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

35

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:222:

```

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro

```

```

      1           5           10           15
Thr Arg Leu Leu Glu Tyr Leu Glu Lys Tyr Glu Glu His Leu
      20           25           30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
      35           40           45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
      50           55           60
5 Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
      65           70           75
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
      85           90           95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
      100           105           110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
      115           120           125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
      130           135           140
10 Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
      145           150           155
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
      165           170           175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
      180           185           190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
      195           200           205
15 Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
      210           215           220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Gly Asp
      225           230           235
Val Phe Arg Glu Leu Arg Asp Arg Trp Asn Ala Thr Ser His His Thr
      245           250           255
Arg Pro

```

20 (2) INFORMATION FOR SEQ ID NO:223:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 257 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:223:

```

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
      1           5           10           15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
      20           25           30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
      35           40           45
30 Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
      50           55           60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
      65           70           75
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
      85           90           95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
      100           105           110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
      115           120           125
35 Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
      130           135           140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
      145           150           155           160

```


Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
 165 170 175
 Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
 180 185 190
 Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
 195 200 205
 Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
 210 215 220
 5 Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Trp Asn
 225 230 235 240
 Ala Thr Ser His His Thr Arg Pro Thr Pro Gln Leu Pro Arg Gly Pro
 245 250 255
 Asn

(2) INFORMATION FOR SEQ ID NO:224:

10

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 267 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:224:

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1 5 10 15
 Thr Arg Leu Leu Glu Tyr Leu Glu Lys Tyr Glu Glu His Leu
 20 25 30
 Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
 35 40 45
 Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
 50 55 60
 20 Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
 65 70 75 80
 Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
 85 90 95
 Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
 100 105 110
 Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
 115 120 125
 25 Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
 130 135 140
 Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
 145 150 155 160
 Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
 165 170 175
 Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
 180 185 190
 Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
 195 200 205
 30 Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
 210 215 220
 Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Gly Asp
 225 230 235 240
 Val Phe Arg Glu Leu Arg Asp Arg Trp Asn Ala Thr Ser His His Thr
 245 250 255
 Arg Pro Thr Pro Gln Leu Pro Arg Gly Pro Asn
 260 265

35

(2) INFORMATION FOR SEQ ID NO:225:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 277 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:225:

```

5  Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
   1      5      10      15
   Thr Arg Leu Leu Leu Glu Tyr Leu Glu Lys Tyr Glu Glu His Leu
      20      25      30
   Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
      35      40      45
   Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
      50      55      60
10  Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
   65      70      75      80
   Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
      85      90      95
   Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
      100      105      110
   Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
      115      120      125
   Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
      130      135      140
15  Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
   145      150      155      160
   Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
      165      170      175
   Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
      180      185      190
   Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
      195      200      205
20  Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
   210      215      220
   Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser His
   225      230      235      240
   Ser Gly Gly Met Asn Arg Ala Tyr Gly Asp Val Phe Arg Glu Leu Arg
      245      250      255
   Asp Arg Trp Asn Ala Thr Ser Ala Ala Thr Arg Pro Thr Pro Gln Leu
      260      265      270
   Pro Arg Gly Pro Asn
      275
25

```

(2) INFORMATION FOR SEQ ID NO:226:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 277 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

30

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:226:

```

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1      5      10      15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
20      25      30
35 Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
   35      40      45
   Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
   50      55      60
   Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn

```

```

65      70      75      80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
85
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
100
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115
5 Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
165
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
195
10 Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
210
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser Ala
225
Arg Asp Ser Gly Pro Ala Glu Asp Gly Ser Arg Ala Val Arg Leu Asn
245
Gly Val Glu Asn Ala Asn Thr Arg Lys Ser Ser Arg Ser Asn Pro Arg
260
15 Gly Arg Arg His Pro
275

```

(2) INFORMATION FOR SEQ ID NO:227:

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 257 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:227:

```

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1      5      10      15
25 Thr Arg Leu Leu Glu Tyr Leu Glu Lys Tyr Glu Glu His Leu
20
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
35
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
50
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
85
30 Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
100
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145
35 Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
165
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
190

```

5 Gly

(i) SEQUENCE CHARACTERISTICS:

- 10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:228:

35

(i) SEQUENCE CHARACTERISTICS:

- (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:229:

```

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1      5      10      15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
20      25      30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
5      35      40      45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
50      55      60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65      70      75      80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
85      90      95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
100      105      110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115      120      125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130      135      140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145      150      155      160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
165      170      175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180      185      190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
195      200      205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
210      215      220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Glu Asn
225      230      235      240
Ala Asn Thr Arg Lys Ser Ser Arg Ser Asn Pro Arg Gly Arg Arg His
245      250      255
20 Pro

```

(2) INFORMATION FOR SEQ ID NO:230:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 248 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:230:

```

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1      5      10      15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
20      25      30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
35      40      45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
50      55      60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65      70      75      80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
85      90      95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
100      105      110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115      120      125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn

```

```

      130      135      140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145      150      155
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
      165      170      175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
      180      185      190
5  Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
      195      200      205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
      210      215      220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ser Glu Asn
225      230      235      240
Ala Asn Thr Arg Lys Ser Ser Arg
      245

```

10 (2) INFORMATION FOR SEQ ID NO:231:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 248 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:231:

```

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1 5 10 15
Thr Arg Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
20 25 30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
35 40 45
20 Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
50 55 60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65 70 75 80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
85 90 95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
100 105 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115 120 125
25 Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130 135 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145 150 155 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
165 170 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180 185 190
30 Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
195 200 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
210 215 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ser Arg Lys
225 230 235 240
Ser Ser Arg Ser Asn Pro Arg Gly
245

```

35 (2) INFORMATION FOR SEQ ID NO:232:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 247 amino acids
 (B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:232:

```

5  Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
   1      5      10      15
   Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
   20      25      30
   Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
   35      40      45
   Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
   50      55      60
   Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
   65      70      75      80
10 Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
   85      90      95
   Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
   100      105      110
   Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
   115      120      125
   Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
   130      135      140
15 Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
   145      150      155      160
   Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
   165      170      175
   Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
   180      185      190
   Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
   195      200      205
   Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
   210      215      220
20 Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser Asn
   225      230      235      240
   Pro Arg Gly Arg Arg His Pro
   245

```

(2) INFORMATION FOR SEQ ID NO:233:

(i) SEQUENCE CHARACTERISTICS:

25 (A) LENGTH: 249 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:233:

```

30 Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
   1      5      10      15
   Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
   20      25      30
   Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
   35      40      45
   Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
   50      55      60
   Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
   65      70      75      80
35 Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
   85      90      95
   Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
   100      105      110

```

Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
 115 120
 Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
 130 135 140
 Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
 145 150 155 160
 Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
 165 170 175
 5 Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
 180 185 190
 Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
 195 200 205
 Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
 210 215 220
 Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Thr Arg
 225 230 235 240
 10 Lys Ser Ser Arg Ser Asn Pro Arg Gly
 245

(2) INFORMATION FOR SEQ ID NO:234:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 277 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

15 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:234:

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1 5 10 15
 Thr Arg Leu Leu Leu Glu Tyr Leu Glu Lys Tyr Glu Glu His Leu
 20 25 30
 Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
 35 40 45
 Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
 50 55 60
 Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
 65 70 75 80
 Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
 85 90 95
 25 Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
 100 105 110
 Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
 115 120 125
 Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
 130 135 140
 Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
 145 150 155 160
 Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
 165 170 175
 30 Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
 180 185 190
 Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
 195 200 205
 Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
 210 215 220
 Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser Thr
 225 230 235 240
 35 Pro Pro Ser Arg Glu Ala Tyr Ser Arg Pro Tyr Ser Val Asp Ser Asp
 245 250 255
 Ser Asp Thr Asn Ala Lys His Ser Ser His Asn Arg Arg Leu Arg Thr
 260 265 270
 Arg Ser Arg Pro Asn

275

(2) INFORMATION FOR SEQ ID NO:235:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 258 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:235:

```

10 Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
    1      5      10      15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Lys Tyr Glu Glu His Leu
    20      25      30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
    35      40      45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50      55      60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
    65      70      75      80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
    85      90      95
15 Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
    100      105      110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
    115      120      125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130      135      140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
    145      150      155      160
20 Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
    165      170      175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
    180      185      190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
    195      200      205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210      215      220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser Thr
    225      230      235      240
25 Pro Pro Ser Arg Glu Ala Tyr Ser Arg Pro Tyr Ser Val Asp Ser Asp
    245      250      255
Ser Asp

```

(2) INFORMATION FOR SEQ ID NO:236:

(i) SEQUENCE CHARACTERISTICS:

- 30 (A) LENGTH: 259 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:236:

```

35 Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
    1      5      10      15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
    20      25      30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu

```

```

      35      40      45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
  50      55      60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
  65      70      75      80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
      85      90      95
5 Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
      100      105      110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
      115      120      125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
      130      135      140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
      145      150      155      160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
      165      170      175
10 Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
      180      185      190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
      195      200      205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
      210      215      220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser Arg
      225      230      235      240
15 Pro Tyr Ser Val Asp Ser Asp Ser Asp Thr Asn Ala Lys His Ser Ser
      245      250      255
His Asn Arg

```

(2) INFORMATION FOR SEQ ID NO:237:

(i) SEQUENCE CHARACTERISTICS:

20

- (A) LENGTH: 257 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:237:

```

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
  1      5      10      15
25 Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
      20      25      30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
      35      40      45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
      50      55      60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
      65      70      75      80
30 Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
      85      90      95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
      100      105      110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
      115      120      125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
      130      135      140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
      145      150      155      160
35 Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
      165      170      175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
      180      185      190

```

Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
 195 200 205
 Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
 210 215 220
 Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Thr Asn
 225 230 235 240
 Ala Lys His Ser Ser His Asn Arg Arg Leu Arg Thr Arg Ser Arg Pro
 245 250 255
 5 Asn

(2) INFORMATION FOR SEQ ID NO:238:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 247 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:238:

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1 5 10 15
 15 Thr Arg Leu Leu Glu Tyr Leu Glu Lys Tyr Glu Glu His Leu
 20 25 30
 Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
 35 40 45
 Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
 50 55 60
 Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
 65 70 75 80
 20 Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
 85 90 95
 Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
 100 105 110
 Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
 115 120 125
 Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
 130 135 140
 Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
 145 150 155 160
 25 Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
 165 170 175
 Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
 180 185 190
 Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
 195 200 205
 Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
 210 215 220
 Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Thr Asn
 225 230 235 240
 30 Ala Lys His Ser Ser His Asn
 245

(2) INFORMATION FOR SEQ ID NO:239:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 248 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:239:

```

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1      5      10      15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
      20      25      30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
 5      35      40      45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
      50      55      60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65      70      75      80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
      85      90      95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
      100      105      110
10 Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
      115      120      125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
      130      135      140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145      150      155      160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
      165      170      175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
15      180      185      190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
      195      200      205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
      210      215      220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser Ser
225      230      235      240
His Asn Arg Arg Leu Arg Thr Arg
      245

```

20

(2) INFORMATION FOR SEQ ID NO:240:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 248 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: unknown

25

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:240:

```

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1      5      10      15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
      20      25      30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
30      35      40      45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
      50      55      60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65      70      75      80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
      85      90      95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
      100      105      110
35 Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
      115      120      125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
      130      135      140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp

```

```

145      150      155      160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
      165      170      175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
      180      185      190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
      195      200      205
5 Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
      210      215      220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Arg Arg
      225      230      235      240
Leu Arg Thr Arg Ser Arg Pro Asn
      245

```

(2) INFORMATION FOR SEQ ID NO:241:

- 10 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 282 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:241:

```

15 Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
   1      5      10      15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Lys Tyr Glu Glu His Leu
   20      25      30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
   35      40      45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
   50      55      60
20 Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
   65      70      75      80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
   85      90      95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
   100      105      110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
   115      120      125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
   130      135      140
25 Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
   145      150      155      160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
   165      170      175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
   180      185      190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
   195      200      205
30 Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
   210      215      220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Arg Val
   225      230      235      240
Gly Gln Cys Thr Asp Ser Asp Val Arg Arg Pro Trp Ala Arg Ser Cys
   245      250      255
Ala His Gln Gly Cys Gly Ala Gly Thr Arg Asn Ser His Gly Cys Ile
   260      265      270
Thr Arg Pro Leu Arg Gln Ala Ser Ala His
   275      280
35

```

(2) INFORMATION FOR SEQ ID NO:242:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 257 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:242:

```

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1      5      10      15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Lys Tyr Glu Glu His Leu
      20      25      30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
      35      40      45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
10      50      55      60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65      70      75      80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
      85      90      95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
      100      105      110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
      115      120      125
15 Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130      135      140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145      150      155      160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
      165      170      175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
      180      185      190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
20      195      200      205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
210      215      220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Arg Val
225      230      235      240
Gly Gln Cys Thr Asp Ser Asp Val Arg Arg Pro Trp Ala Arg Ser Cys
      245      250      255
Ala

```

25

(2) INFORMATION FOR SEQ ID NO:243:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 259 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

30 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:243:

```

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1      5      10      15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
      20      25      30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
35      35      40      45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
50      55      60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65      70      75      80

```

- 225 -

225 230 235 240
Arg Asn Ser His Gly Cys Ile Thr Arg Pro Leu Arg Gln Ala Ser Gln
 245 250 255

His

(2) INFORMATION FOR SEO ID NO:245:

5

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 282 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:245:

	Met 1	Ser	Pro	Ile	Leu 5	Gly	Tyr	Trp	Lys	Ile 10	Lys	Gly	Leu	Val	Gln 15	Pro
	Thr	Arg	Leu	Leu 20	Leu	Glu	Tyr	Leu	Glu 25	Glu	Lys	Tyr	Glu	Glu 30	His	Leu
	Tyr	Glu	Arg 35	Asp	Glu	Gly	Asp 40	Lys	Trp	Arg	Asn	Lys 45	Lys	Phe	Glu	Leu
15	Gly 50	Leu	Glu	Phe	Pro	Asn 55	Leu	Pro	Tyr	Tyr	Ile 60	Asp	Gly	Asp	Val	Lys
	Leu 65	Thr	Gln	Ser	Met 70	Ala	Ile	Ile	Arg	Tyr	Ile 75	Ala	Asp	Lys	His	Asn 80
	Met	Leu	Gly	Gly 85	Cys	Pro	Lys	Glu	Arg	Ala 90	Glu	Ile	Ser	Met	Leu 95	Glu
	Gly	Ala	Val 100	Leu	Asp	Ile	Arg	Tyr	Gly 105	Val	Ser	Arg	Ile	Ala	Tyr	Ser
	Lys	Asp 115	Phe	Glu	Thr	Leu	Lys	Val 120	Asp	Phe	Leu	Ser 125	Lys	Leu	Pro	Glu
20	Met 130	Leu	Lys	Met	Phe	Glu	Asp 135	Arg	Leu	Cys	His 140	Lys	Thr	Tyr	Leu	Asn
	Gly 145	Asp	His	Val	Thr	His 150	Pro	Asp	Phe	Met	Leu 155	Tyr	Asp	Ala	Leu	Asp 160
	Val	Val	Leu	Tyr 165	Met	Asp	Pro	Met	Cys	Leu 170	Asp	Ala	Phe	Pro	Lys 175	Leu
	Val	Cys	Phe 180	Lys	Lys	Arg	Ile	Glu	Ala 185	Ile	Pro	Gln	Ile	Asp 190	Lys	Tyr
25	Leu	Lys	Ser 195	Ser	Lys	Tyr	Ile	Ala 200	Trp	Pro	Leu	Gln	Gly 205	Trp	Gln	Ala
	Thr	Phe 210	Gly	Gly	Gly	Asp	His 215	Pro	Pro	Lys	Ser 220	Asp	Leu	Val	Pro	Arg
	Gly 225	Ser	Pro	Gly	Ile	Pro 230	Gly	Ser	Thr	Arg	Ala 235	Ala	Ala	Ser	Arg	Tyr 240
	Lys	His	Asp	Ile 245	Gly	Cys	Asp	Ala	Gly	Val 250	Asp	Lys	Lys	Ser	Ser 255	Ser
	Val	Arg	Gly 260	Gly	Cys	Gly	Ala	His 265	Ser	Ser	Pro	Pro	Arg	Ala 270	Gly	Arg
30	Gly	Pro	Arg 275	Gly	Thr	Met	Val	Ser 280	Arg	Leu						

(2) INFORMATION FOR SEO ID NO:246:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 262 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: unknown

35

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:246:

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1 5 10 15
 Thr Arg Leu Leu Glu Tyr Leu Glu Lys Tyr Glu Glu His Leu
 20 25 30
 Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
 35 40 45
 Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
 50 55 60
 5 Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
 65 70 75 80
 Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
 85 90 95
 Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
 100 105 110
 Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
 115 120 125
 10 Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
 130 135 140
 Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
 145 150 155 160
 Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
 165 170 175
 Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
 180 185 190
 Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
 195 200 205
 15 Thr Phe Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
 210 215 220
 Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Arg Tyr
 225 230 235 240
 Lys His Asp Ile Gly Cys Asp Ala Gly Val Asp Lys Lys Ser Ser Ser
 245 250 255
 Val Arg Gly Gly Cys Gly
 260

20

(2) INFORMATION FOR SEQ ID NO:247:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 264 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

25

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:247:

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1 5 10 15
 Thr Arg Leu Leu Glu Tyr Leu Glu Lys Tyr Glu Glu His Leu
 20 25 30
 Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
 35 40 45
 30 Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
 50 55 60
 Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
 65 70 75 80
 Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
 85 90 95
 Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
 100 105 110
 35 Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
 115 120 125
 Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
 130 135 140
 Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp

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145          150          155          160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
          165          170          175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
          180          185          190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
          195          200          205
5 Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
          210          215          220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Gly Cys
225          230          235          240
Asp Ala Gly Val Asp Lys Lys Ser Ser Ser Val Arg Gly Gly Cys Gly
          245          250          255
Ala His Ser Ser Pro Pro Arg Ala
          260

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10 (2) INFORMATION FOR SEQ ID NO:248:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 259 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:248:

```

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1      5      10      15
Thr Arg Leu Leu Glu Tyr Leu Glu Lys Tyr Glu Glu His Leu
20      25      30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
35      40      45
20 Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
50      55      60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65      70      75      80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
85      90      95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
100      105      110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115      120      125
25 Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130      135      140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145      150      155      160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
165      170      175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180      185      190
30 Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
195      200      205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
210      215      220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Gly Ala
225      230      235      240
His Ser Ser Pro Pro Arg Ala Gly Arg Gly Pro Arg Gly Thr Met Val
245      250      255
Ser Arg Leu

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35

(2) INFORMATION FOR SEQ ID NO:249:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 44 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:249:

Ser	Gly	Ser	Pro	Pro	Cys	Cys	Cys	Ser	Trp	Gly	Arg	Phe	Met	Gln	Gly
1				5				10						15	
Gly	Leu	Phe	Gly	Arg	Thr	Asp	Gly	Cys	Gly	Ala	His	Arg	Asn	Arg	
			20			25						30			
Thr	Ser	Ala	Ser	Leu	Glu	Pro	Pro	Ser	Ser	Asp	Tyr				
		35				40									

10 (2) INFORMATION FOR SEQ ID NO:250:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 40 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:250:

Ser	His	Ser	Gly	Gly	Met	Asn	Arg	Ala	Tyr	Gly	Asp	Val	Phe	Arg	Glu
1				5				10						15	
Leu	Arg	Asp	Arg	Trp	Asn	Ala	Thr	Ser	His	His	Thr	Arg	Pro	Thr	Pro
			20			25						30			
Gln	Leu	Pro	Arg	Gly	Pro	Asn	Ser								
		35				40									

20 (2) INFORMATION FOR SEQ ID NO:251:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

25 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:251:

Asp	Thr	Asn	Ala	Lys	His	Ser	Ser	His	Asn	Arg	Arg	Leu	Arg	Thr	Arg
1				5				10						15	
Ser	Arg	Pro	Asn	Gly											
			20												

30 (2) INFORMATION FOR SEQ ID NO:252:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:252:

Cys	Gly	Ala	Gly	Thr	Arg	Asn	Ser	His	Gly	Cys	Ile	Thr	Arg	Pro	Leu
1				5				10						15	

Arg Gln Ala Ser Ala His Gly
20

(2) INFORMATION FOR SEQ ID NO:253:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

- 10 (A) NAME/KEY: Modified Site
(B) LOCATION: 1
(D) OTHER INFORMATION: "Xaa=Ser or Thr"

- (A) NAME/KEY: Modified Site
(B) LOCATION: 3
(D) OTHER INFORMATION: "Xaa=Arg or Lys"

- 15 (A) NAME/KEY: Modified Site
(B) LOCATION: 4
(D) OTHER INFORMATION: "Xaa=Lys or Arg"

- (A) NAME/KEY: Modified Site
(B) LOCATION: 6
(D) OTHER INFORMATION: "Xaa=Ser or Leu"

- (A) NAME/KEY: Modified Site
(B) LOCATION: 7
(D) OTHER INFORMATION: "Xaa=Arg, Ile, Val or Ser"

- 20 (A) NAME/KEY: Modified Site
(B) LOCATION: 8
(D) OTHER INFORMATION: "Xaa=Ser, Tyr, Phe or His"

- (A) NAME/KEY: Modified Site
(B) LOCATION: 10
(D) OTHER INFORMATION: "Xaa=Phe, His or Arg"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:253:

25 Xaa Thr Xaa Xaa Ser Xaa Xaa Xaa Asn Xaa Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:254:

(i) SEQUENCE CHARACTERISTICS:

- 30 (A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

- 35 (A) NAME/KEY: Modified Site
(B) LOCATION: 2
(D) OTHER INFORMATION: "Xaa=Ser, Ala or Gly"

- (A) NAME/KEY: Modified Site
(B) LOCATION: 4
(D) OTHER INFORMATION: "Xaa=Val or Gln"

(A) NAME/KEY: Modified Site
 (B) LOCATION: 7
 (D) OTHER INFORMATION: "Xaa=Pro, Gly or Ser"

(A) NAME/KEY: Modified Site
 (B) LOCATION: 8
 (D) OTHER INFORMATION: "Xaa=Trp or Tyr"

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:254:

Asp Xaa Asp Xaa Arg Arg Xaa Xaa
 1 5

(2) INFORMATION FOR SEQ ID NO:255:

10

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 10 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide
 (ix) FEATURE:

15

(A) NAME/KEY: Modified Site
 (B) LOCATION: 7
 (D) OTHER INFORMATION: "Xaa=Ala or Phe"

(A) NAME/KEY: Modified Site
 (B) LOCATION: 8
 (D) OTHER INFORMATION: "Xaa=Arg or His"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:255:

20

Val Arg Ser Gly Cys Gly Xaa Xaa Ser Ser
 1 5 10

(2) INFORMATION FOR SEQ ID NO:256:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 11 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

25

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:256:

Asn Thr Arg Lys Ser Ser Arg Ser Asn Pro Arg
 1 5 10

30

(2) INFORMATION FOR SEQ ID NO:257:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 11 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: unknown

35

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:257:

Ser Thr Lys Arg Ser Leu Ile Tyr Asn His Arg

1 5 10

(2) INFORMATION FOR SEQ ID NO:258:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:258:

Ser Thr Gly Arg Lys Val Phe Asn Arg Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:259:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:259:

Thr Asn Ala Lys His Ser Ser His Asn Arg Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:260:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS :

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:260:

25 Asp Ser Asp Val Arg Arg Pro Trp
1 5

(2) INFORMATION FOR SEQ ID NO:261:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS :

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:261:

Ala Ala Asp Gln Arg Arg Gly Trp
1 5

(2) INFORMATION FOR SEQ ID NO:262:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids

- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:262:

5 Asp Gly Arg Gly Gly Arg Ser Tyr
1 5

(2) INFORMATION FOR SEQ ID NO:263:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:263:

Arg Val Arg Ser
1

15

(2) INFORMATION FOR SEQ ID NO:264:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

20 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:264:

Ser Val Arg Ser Gly Cys Gly Phe Arg Gly Ser Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO:265:

25 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 11 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:265:

30 Ser Val Arg Gly Gly Cys Gly Ala His Ser Ser
1 5 10

35

WHAT IS CLAIMED IS:

1. A purified protein which specifically binds to a gastro-intestinal tract receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI.

2. A protein which binds specifically to a gastro-intestinal transport receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, in which the protein comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-55 or a binding portion thereof.

3. A protein which binds specifically to a gastro-intestinal transport receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, in which the amino acid sequence of the protein is selected from the group consisting of SEQ ID NOS:1-55, or a binding portion thereof.

4. The protein of claim 2 which comprises the amino acid sequence substantially as set forth in: SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 30, SEQ ID NO: 43, SEQ ID NO: 46, or SEQ ID NO: 52, or a binding portion thereof.

5. The protein of claim 3, the amino acid sequence of which consists of the amino acid sequence substantially as set forth in: SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 30, SEQ ID NO: 43, SEQ ID NO: 46, or SEQ ID NO: 52, or a binding portion thereof.

6. A protein of not more than 50 amino acids in length which specifically binds to a gastro-intestinal transport receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, in which the protein includes, positioned anywhere along its sequence, the contiguous amino

acid sequence of: Xaa₁ Thr Xaa₂ Xaa₃ Ser Xaa₄ Xaa₅ Xaa₆ Asn Xaa₇ Arg (SEQ ID NO:253), where Xaa₁ is Ser or Thr; Xaa₂ is Arg or Lys; Xaa₃ is Lys or Arg; Xaa₄ is Ser or Leu; Xaa₅ is Arg, Ile, Val, or Ser; Xaa₆ is Ser, Tyr, Phe, or His; and Xaa₇ is Pro, His or Arg.

7. The protein of claim 6 which is not more than 40 amino acids in length.

10 8. The protein of claim 6 which is not more than 30 amino acids in length.

9. The protein of claim 6 which is not more than 20 amino acids in length.

15

10. A protein of not more than 50 amino acids in length which specifically binds to a gastro-intestinal transport receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, in which the protein includes, positioned anywhere along its sequence, the contiguous amino acid sequence of: Asp Xaa₁ Asp Xaa₂ Arg Arg Xaa₃ Xaa₄ (SEQ ID NO:254) where Xaa₁ is Ser, Ala, or Gly; Xaa₂ is Val or Gln; Xaa₃ is Pro, Gly, or Ser; and Xaa₄ is Trp or Tyr.

25 11. The protein of claim 10 which is not more than 40 amino acids in length.

12. The protein of claim 10 which is not more than 30 amino acids in length.

30

13. The protein of claim 10 which is not more than 20 amino acids in length.

14. A protein of not more than 50 amino acids in length which specifically binds to a gastro-intestinal transport receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, in which the protein includes,

positioned anywhere along its sequence, the contiguous amino acid sequence of: Val Arg Ser Gly Cys Gly Xaa₁ Xaa₂ Ser Ser (SEQ ID NO:255), where Xaa₁ is Ala or Phe; and Xaa₂ is Arg or His.

5

15. The protein of claim 14 which is not more than 40 amino acids in length.

16. The protein of claim 14 which is not more than
10 30 amino acids in length.

17. The protein of claim 14 which is not more than 20 amino acids in length.

15 18. A protein of not more than 50 amino acids in length which specifically binds to a gastro-intestinal transport receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, in which the protein includes, positioned anywhere along its sequence, the contiguous amino
20 acid sequence of: NTRKSSRSNPR (SEQ ID NO:256) or STKRSLIYNHR (SEQ ID NO:257) or STGRKVFNRR (SEQ ID NO:258) or TNAKHSSHNR (SEQ ID NO:259).

19. A protein of not more than 50 amino acids in
25 length which specifically binds to a gastro-intestinal transport receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, in which the protein includes, positioned anywhere along its sequence, the contiguous amino acid sequence of: DSDVRRPW (SEQ ID NO:260) or AADQRRGW (SEQ
30 ID NO:261) or DGRGGRSY (SEQ ID NO:262).

20. A protein of not more than 50 amino acids in length which specifically binds to a gastro-intestinal transport receptor selected from the group consisting of
35 HPT1, hPEPT1, D2H, and hSI, in which the protein includes, positioned anywhere along its sequence, the contiguous amino

acid sequence of: RVRS (SEQ ID NO:263) or SVRSGCGFRGSS (SEQ ID NO:264) or SVRGGCGAHSS (SEQ ID NO:265).

21. The protein of claim 1, 2, 3, 6, 10, 14, 18,
5 19, or 20 which is purified.

22. A composition comprising the protein of claim
1, 2, 3, 6, 10, 14, 18, 19, or 20, bound to a material
comprising an active agent, said active agent being of value
10 in the treatment of a mammalian disease or disorder.

23. The composition of claim 22 in which the
active agent is a drug.

15 24. The composition of claim 22 in which the
material is a particle containing the active agent.

25. The composition of claim 22 in which the
material is a slow-release device containing the drug.
20

26. The composition of claim 22 in which the
protein is covalently or noncovalently bound to the material.

27. A composition comprising a chimeric protein
25 bound to a material comprising an active agent, in which the
chimeric protein comprises a sequence selected from the group
consisting of SEQ ID NOS:1-55 or a binding portion thereof
fused via a covalent bond to an amino acid sequence of a
second protein, in which the active agent is of value in the
30 treatment of a mammalian disease or disorder.

28. A composition comprising the protein of claim
1, 2, 3, 6, 10, 14, 18, 19, or 20 covalently bound to a
particle containing a drug.
35

29. A composition comprising the protein of claim
1, 2, 3, 6, 10, 14, 18, 19, or 20 covalently bound to a drug.

30. The composition of claim 22 which facilitates the transport of the active agent through human or animal gastro-intestinal tissue.

5 31. A method of delivering an active agent *in vivo* comprising administering to a subject a purified composition of claim 22.

32. A method of delivering a drug to a subject
10 comprising administering to the subject a purified composition of claim 30.

33. A method of delivering a drug to a subject comprising administering to the subject a purified
15 composition of claim 31.

34. The method according to claim 31 in which the administering is oral.

20 35. The method according to claim 31 in which the active agent is a drug.

36. The method according to claim 31 in which the subject is a human.

25 37. The method according to claim 35 in which the subject is a human.

38. The method according to claim 31 in which said
30 composition facilitates the transport of the active agent through human or animal gastro-intestinal tissue.

39. The method according to claim 33 in which the administering is oral.

35

40. A pharmaceutical composition comprising the composition of claim 22 in a pharmaceutically acceptable carrier suitable for use in humans *in vivo*.

5 41. A chimeric protein comprising at least 6 contiguous amino acids of an amino acid sequence selected from the group consisting of SEQ ID NOS:1-55, that specifically bind to a gastro-intestinal tract receptor, fused via a covalent bond to an amino acid sequence of a
10 second protein.

 42. An antibody which is capable of immunospecifically binding the protein of claim 2, 3, 6, 10, 14, 18, 19 or 20.
15

 43. A molecule comprising a fragment of the antibody of claim 42, which fragment is capable of immunospecifically binding said protein.

20 44. A purified derivative of the protein of claim 1 or 2, which displays one or more functional activities of said protein.

 45. The derivative of claim 44 which is able to be
25 bound by an antibody directed against said protein.

 46. A fragment of the protein of claim 2 comprising a domain of said protein.

30 47. A fragment of the protein of claim 3 comprising a domain of said protein.

 48. A nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID
35 NOS:110-163.

49. A nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS:55-109.

5 50. An isolated nucleic acid comprising a nucleotide sequence encoding the protein of claim 1.

51. A nucleic acid comprising a nucleotide sequence encoding the protein of claim 2, 3, 6, 10, 14, 18,
10 19 or 20.

52. The nucleic acid of claim 51 which is a DNA.

53. The nucleic acid of claim 48 or 49 which is
15 isolated.

54. The nucleic acid of claim 51 which is isolated.

20 55. An isolated nucleic acid comprising a nucleotide sequence complementary to the nucleotide sequence of claim 57.

56. An isolated nucleic acid comprising a
25 nucleotide sequence encoding a fragment of the protein of claim 1, 2, or 3, which fragments bind to said gastrointestinal tract receptor.

57. A nucleic acid comprising a nucleotide
30 sequence encoding the chimeric protein of claim 41.

58. A nucleic acid comprising a nucleotide sequence encoding the fragment of claim 47.

35 59. The nucleic acid of claim 57 which is isolated.

60. The nucleic acid of claim 58 which is isolated.

61. A recombinant cell containing the nucleic acid of claim 48, 49 or 50.

62. A recombinant cell containing the nucleic acid of claim 51.

10 63. A recombinant cell containing the nucleic acid of claim 57.

64. A method of producing a protein comprising growing a recombinant cell containing the nucleic acid of 15 claim 48, 49 or 50 such that the encoded protein is expressed by the cell, and recovering the expressed protein.

65. A method of producing a protein comprising growing a recombinant cell containing the nucleic acid of 20 claim 51 such that the encoded protein is expressed by the cell, and recovering the expressed protein.

66. A method of producing a protein comprising growing a recombinant cell containing the nucleic acid of 25 claim 57 such that the encoded protein is expressed by the cell, and recovering the expressed protein.

67. The product of the process of claim 64.

30 68. The product of the process of claim 65.

69. The product of the process of claim 66.

70. A pharmaceutical composition comprising a 35 therapeutically effective amount of a composition comprising the protein of claim 1, 2, 3, 6, 10, 14, 18, 19, or 20; and a pharmaceutically acceptable carrier.

71. The chimeric protein of claim 41 in which said second protein is a drug.

72. A nucleic acid comprising a nucleotide
5 sequence encoding the protein of claim 71.

73. A pharmaceutical composition comprising a therapeutically effective amount of the protein of claim 71, and a pharmaceutically acceptable carrier.

10

74. A pharmaceutical composition comprising a therapeutically effective amount of the nucleic acid of claim 78.

15

75. A method of delivering a drug to a subject comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of claim 80.

20

76. A method of treating or preventing a disease or disorder comprising administering to a subject in which such treatment or prevention is desired a therapeutically effective amount of the composition of claim 23.

25

77. A method of treating or preventing a disease or disorder comprising administering to a subject in which such treatment or prevention is desired a therapeutically effective amount of the composition of claim 28.

30

78. A method of treating or preventing a disease or disorder comprising administering to a subject in which such treatment or prevention is desired a therapeutically effective amount of the composition of claim 29.

35

79. The method according to claim 76 in which the disease or disorder is selected from the group consisting of:

hypertension, diabetes, osteoporosis, hemophilia, anemia, cancer, migraines, and angina pectoris.

80. The method according to claim 76 in which the
5 subject is a human.

81. A composition comprising the protein of claim
1, 2, 3, 6, 10, 14, 18, 19, 20, or 46 wherein the protein is
coated onto or absorbed onto or covalently bonded to the
10 surface of a nano- or microparticle.

82. A nano- or microparticle formed from the
protein of claim 1, 2, 3, 6, 10, 14, 18, 19, 20, or 46.

15 83. The composition of claim 87, wherein the nano-
or microparticle is a drug-loaded or drug-encapsulating nano-
or microparticle.

84. A method of detecting or measuring the level
20 of a gastro-intestinal tract receptor in a sample, comprising
contacting a sample suspected of containing a gastro-
intestinal tract receptor with the protein of claim 1, 2, 3,
6, 10, 14, 18, 19, 20, or 46 under conditions conducive to
binding between the protein and any of said receptor in said
25 sample, and detecting or measuring any of said binding that
occurs, in which the detected or measured amount of binding
indicates the presence or amount of the receptor in the
sample.

30 85. A method of identifying a molecule that
specifically binds to a ligand selected from the group
consisting of the protein of claim 1, 2, 3, 6, 10, 14, 18, or
19, a fragment of said protein comprising a domain of the
protein, and a nucleic acid encoding said protein or
35 fragment, comprising

(a) contacting said ligand with a plurality of molecules under conditions conducive to binding between said ligand and the molecules; and

(b) identifying a molecule within said plurality
5 that specifically binds to said ligand.

86. An isolated nucleic acid encoding a fragment of a gastro-intestinal tract receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, or encoding a
10 chimeric protein comprising said fragment, said fragment consisting essentially of the extracellular domain of the receptor.

87. A cell containing and capable of expressing a
15 recombinant nucleic acid encoding a fragment of a gastro-intestinal tract receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, or encoding a chimeric protein comprising said fragment, said fragment consisting essentially of the extracellular domain of the receptor.

20

88. The cell of claim 87 which contains an expression vector comprising a nucleotide sequence encoding said fragment operably linked to a heterologous promoter.

25

89. A method for identifying a molecule that specifically binds to a gastro-intestinal tract receptor comprising contacting a fragment of the receptor, or a chimeric protein comprising said fragment, with a plurality of test molecules under conditions conducive to binding
30 between said fragment or protein and the molecules, and identifying a molecule within said plurality that specifically binds to said fragment or protein, in which the fragments consist essentially of the extracellular domain of the receptor.

35

90. The composition of claim 22 for use as a medicament.

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ATG TCC CCT ATA CTA GGT TAT TGG AAA ATT AAG GGC CTT GTG CAA CCC Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro 1 5 10 15	48
ACT CGA CTT CTT TTG GAA TAT CTT GAA GAA AAA TAT GAA GAG CAT TTG Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu 20 25 30	96
TAT GAG CGC GAT GAA GGT GAT AAA TGG CGA AAC AAA AAG TTT GAA TTG Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu 35 40 45	144
GGT TTG GAG TTT CCC AAT CTT CCT TAT TAT ATT GAT GGT GAT GTT AAA Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys 50 55 60	192
TTA ACA CAG TCT ATG GCC ATC ATA CGT TAT ATA GCT GAC AAG CAC AAC Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn 65 70 75 80	240
ATG TTG GGT GGT TGT CCA AAA GAG CGT GCA GAG ATT TCA ATG CTT GAA Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu 85 90 95	288
GGA GCG GTT TTG GAT ATT AGA TAC GGT GTT TCG AGA ATT GCA TAT AGT Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser 100 105 110	336
AAA GAC TTT GAA ACT CTC AAA GTT GAT TTT CTT AGC AAG CTA CCT GAA Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu 115 120 125	384
ATG CTG AAA ATG TTC GAA GAT CGT TTA TGT CAT AAA ACA TAT TTA AAT Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn 130 135 140	432
GGT GAT CAT GTA ACC CAT CCT GAC TTC ATG TTG TAT GAC GCT CTT GAT Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp 145 150 155 160	480
GTT GTT TTA TAC ATG GAC CCA ATG TGC CTG GAT GCG TTC CCA AAA TTA Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu 165 170 175	528
GTT TGT TTT AAA AAA CGT ATT GAA GCT ATC CCA CAA ATT GAT AAG TAC Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr 180 185 190	576
TTG AAA TCC AGC AAG TAT ATA GCA TGG CCT TTG CAG GGC TGG CAA GCC Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala 195 200 205	624
ACG TTT GGT GGT GGC GAC CAT CCT CCA AAA TCG GAT CTG GTT CCG CGT Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg 210 215 220	672
GGA TCC CCA GGA ATT CCC GGG TCG ACT CGA GCG GCC GCA TCG TGA Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser 225 230 235	717

FIG.23

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DAB10 AA SEQ. POSITION	KNOWN PROTEIN	HOMOLOGOUS SEQ. POSITION
13-34	1,3-BETA-GLUCANASE	231-252
3-11	PHOTOSYNTHETIC REACTION CENTER	20-28
16-27		128-139
28-35	MYB PROTO-ONCOGENE PROTEIN	131-138
5-18		32-45
23-36	LYSOZYME MUTANT	130-143
28-35	LIPASE	400-407
3-15		159-171
3-37	TRYPSIN	169-203
13-34	1,3-1,4-BETA-GLUCANASE	232-253
4-10	LACTATE DEHYDROGENASE	190-196
11-7		244-250
4-10	APO-LACTATE DEHYDROGENASE	190-196
11-17		244-250
4-10	LACTATE DEHYDROGENASE	191-197
11-17		245-251
16-26	OVOTRANSFERRIN	240-250
23-36	GENOME POLYPROTEIN MATRIX PROTEIN	1022-1035
14-20	ROUS SARCOMA VIRUS	43-49
2-12		13-23
14-20	HYPOTHETICAL PROTEIN-AVIAN LEUKOSIS VIRUS	43-49
4-20	T CELL RECEPTOR DELTA CHAIN VARIABLE REGION	1-4
14-18		12-16
2-12	GAG POLYPROTEIN-AVIAN ENDOGENOUS VIRUS RAV-0	139-149
14-20		169-175
	p19 PROTEIN-AVIAN ERYTHROBLASTOSIS VIRUS	189-199
14-20		219-225
7-19	ALI PROTEIN-POTATO YELLOW MOSAIC VIRUS	222-234
3-22	ENDO-1,4-BETA GLUCANASE	186-205
6-18	I α PROTEIN-BROME MOSAIC VIRUS	430-442
2-12	GAG POLYPROTEIN-FUJINAMI SARCOMA VIRUS	186-196
14-22		216-222
2-12	GAG PROTEIN-ROUS SARCOMA VIRUS	190-200
14-20		220-226
1-12	CORTICOTROPIN-LIKE INTERMEDIATE LOBE PEPTIDE	7-18
1-22	GENE PRODUCT (CAENORHABDITIS ELEGANS)	4-25
31-37	T CELL RECEPTOR DELTA CHAIN	56-62
26-39		12-15
26-37	LYSOZYME MUTANT	133-144

FIG.22

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DCX8A SEQ. POSITION	KNOWN PROTEIN	HOMOLOGOUS SEQ. POSITION
1-21	PUTATIVE RNA BINDING PROTEIN	230-250
6-18	HYPOTHETICAL PROTEIN-MOUSE PIR	1-13
2-13	NEUROPEPTIDE PRECURSOR	80-91
7-21	orf3-HUMAN	5-19
1-21	RNA-BINDING PROTEIN	230-250
13-16	COLLAGEN	25-28
7-19	PROBABLE CELL GROWTH OR DIFFERENTIATION REGULATOR	306-318
2-13	RIBOSOMAL PROTEIN S2	14-25
14-17		182-185
2-22	CAENORHABDITIS ELEGANS	296-316
1-12	HOMOSAPIENS	61-72
14-21		116-123
2-16	XYLULOSE KINASE	16-30
8-15	T CELL RECEPTOR DELTA CHAIN	55-62
5-8		12-15
8-17	SEQ. 43 FROM PATENT US	12-21

FIG.21C

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DCX8A SEQ. POSITION	KNOWN PROTEIN	HOMOLOGOUS SEQ. POSITION
24-38	XYLULOSE KINASE	16-30
24-39	CAENORHABDITIS ELEGANS	57-72
26-42		65-81
27-33	HYPOTHETICAL PROTEIN-PHAGE BZ13	22-28
35-39		31-35
30-42	CEREBELLIN-LIKE GLYCOPROTEIN	2-14
8-22	DNA PRIMASE	170-184
2-7		76-81
5-21	COAT PROTEIN (BEAN COMMON MOSAIC VIRUS)	12-28
5-21	COAT PROTEIN (BEAN COMMON MOSAIC VIRUS)	33-49
5-21		19-35
5-21	POLYPROTEIN (BEAN COMMON MOSAIC VIRUS)	215-231
5-21		39-55
5-21	Nib PROTEINLCOAT PROTEIN (COWPEA APHID-BOME MOSAIC VIRUS)	92-108
2-13	MHC CLASS 1 PIPI (PITHECIA)	111-122
14-22		236-334
3-19	TALIN (CAENORHABDITIS ELEGANS)	1538-1554
2-9	ACETAMIDASE PIR	359-366
9-20		483-494
10-16	RHIZOBIONS ETLI STRAIN	134-140
17-30		173-186
31-39		200-208
2-11	NEUROTOXIN 1 (TOXIN B) A. STOKESI	7-16
12-33		26-47
21-27	SUID HERPES VIRUS 1 EARLY PROTEIN	425-432
30-43		51-64
13-42	RICE cDNA PARTIAL SEQUENCE	50-151
8-15	FUSION PROTEIN	24-31
4-8		16-20
1-22	SECRETIN PRECURSOR, N-PROSECRETIN, SECRETIN-AMIDE	18-39
11-22	T-CELL RECEPTOR V BETA CHAIN	15-26
5-11		3-9
9-22	HYPOTHETICAL PROTEIN	275-288
2-8		251-257

FIG.21B

SUBSTITUTE SHEET (RULE 26)

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DCX8AA SEQ. POSITION	KNOWN PROTEIN	HOMOLOGOUS SEQ. POSITION
20-27	ENDO-1,4-BETA-D-GLUCANASE	78-85
30-37		221-228
21-34	P-HYDROXYBENZOATE HYDROXYLASE	285-298
5-15		54-64
7-21	CYTOCHROME	50-64
7-21	CYTOCHROME C3	50-64
	TRIMETHYLARNINE DEHYDROGENASE	208-219
32-43		396-407
30-37	Gag-JunD FUSION PROTEIN	24-31
26-30		16-20
23-44	SECRETIN PRECURSOR, N-PROSECRETIN, SECRETIN AINIDE	18-39
33-44	T-CELL RECEPTOR V BETA CHAIN	15-26
27-33		3-9
23-44	SECRETIN PRECURSOR PIR	18-39
31-44	HYPOTHETICAL PROTEIN V (SYNECHOCYSTIS)	275-288
24-30		251-257
23-43	PUTATIVE RNA BINDING PROTEIN	230-250
28-40	Mu SON OF SEVENLESS 1	1-13
24-35	NEUROPEPTIDE PRECURSOR	80-91
29-43		5-19
23-43	RNA-BINDING PROTEIN (MACACAFASCICULARIS)	230-250
23-43	RNA-BINDING PROTEIN (HOMOSAPIENS)	230-250
23-43	AUTOSOMAL GENE-AZOOSPERMIA FACTOR	230-250
25-38	COLLAGEN	25-28
24-35		4-15
29-41	PROBABLE CELL GROWTH REGULATOR	306-318
24-35	RIBOSOMAL PROTEIN S2	24-35
T6-39		182-185
24-44	CAENORHABDITIS ELEGANS	296-316
23-34	pid:e208155 (HOMO SAPIENS)	61-72
36-43		116-123

FIG.21A

SUBSTITUTE SHEET (RULE 26)

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P31 AA SEQ. POSITION	KNOWN PROTEIN	HOMOLOGOUS SEQ. POSITION
12-34	FASCICULIN 2	10-32
4-12	MESENTERICOPEPTIDASE	54-62
15-31		175-191
26-39	CORE PROTEIN (HEPATITIS C VIRUS)	5-18
26-39		11-24
26-39		21-34
26-39		38-51
23-30		39-55
25-39		41-55
26-39		51-64
16-39	PT-NANBH POLYPROTEIN N-TERMINUS	51-64
28-40	AL2 PROTEIN (CAENORHABDITISELEGANS)	70-82
26-38	CAPSID PROTEIN (HEPATITIS C VIRUS TYPE 3g)	48-60
26-39	GENOME POLYPROTEIN (HEPATITIS C VIRUS)	57-70

FIG.20

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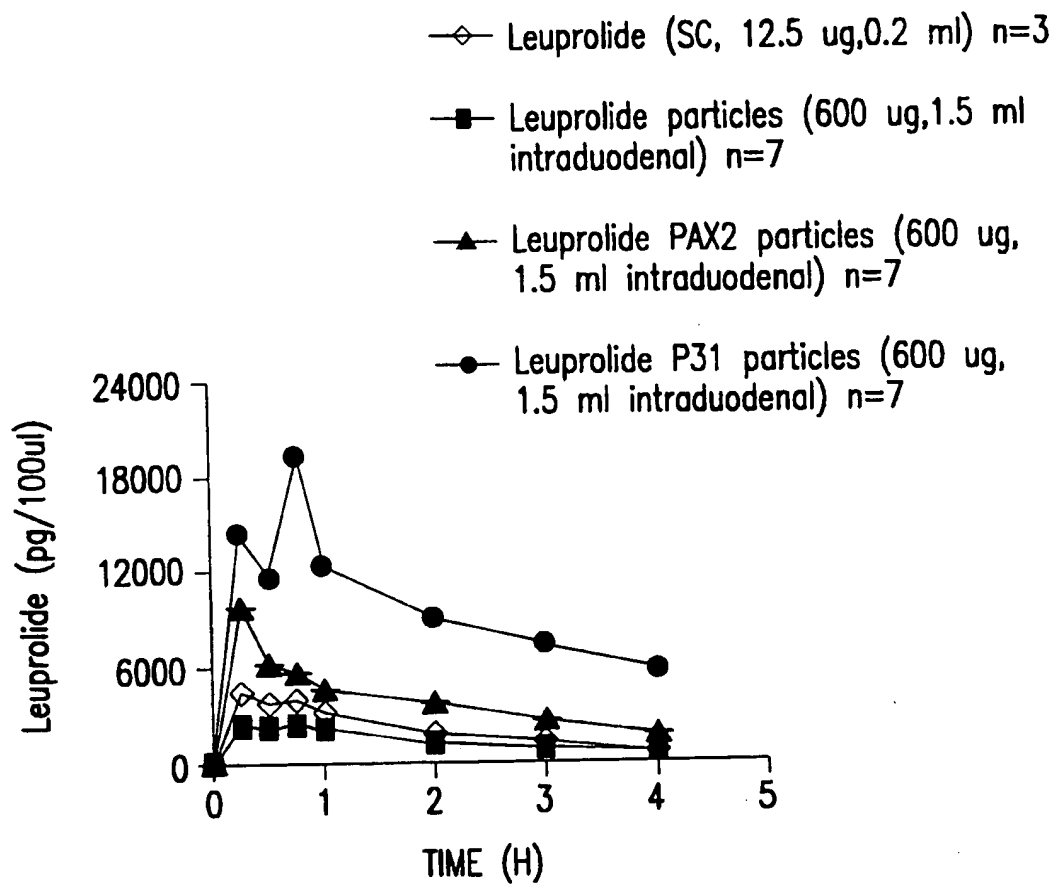


FIG. 19

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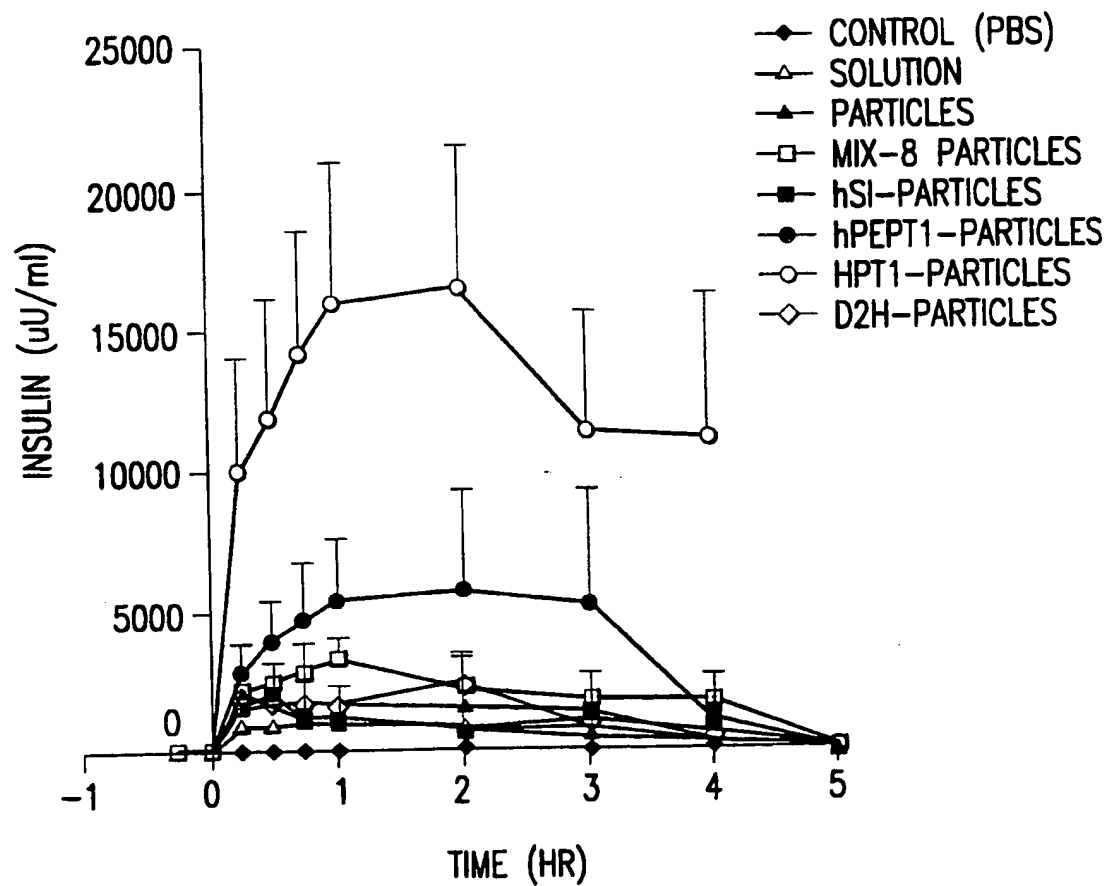


FIG.18B

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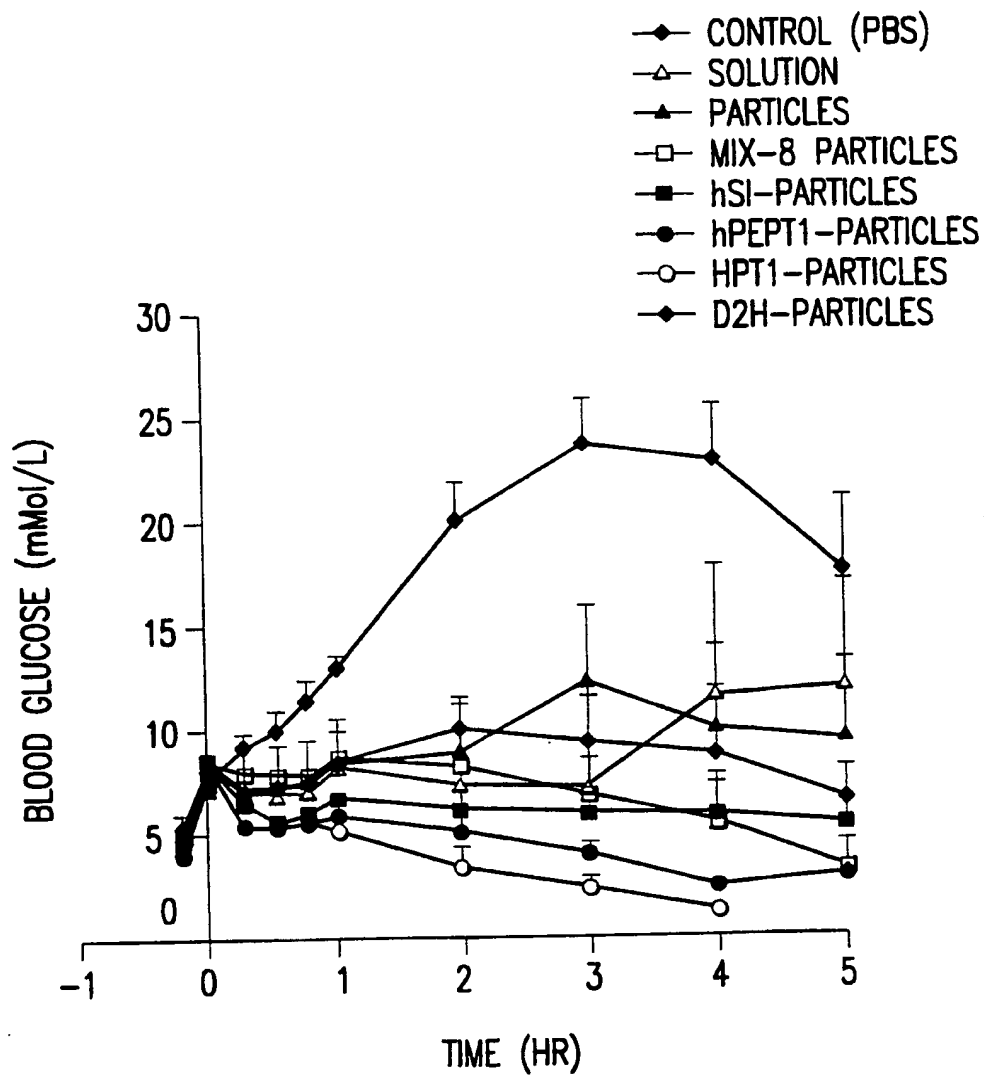


FIG. 18A

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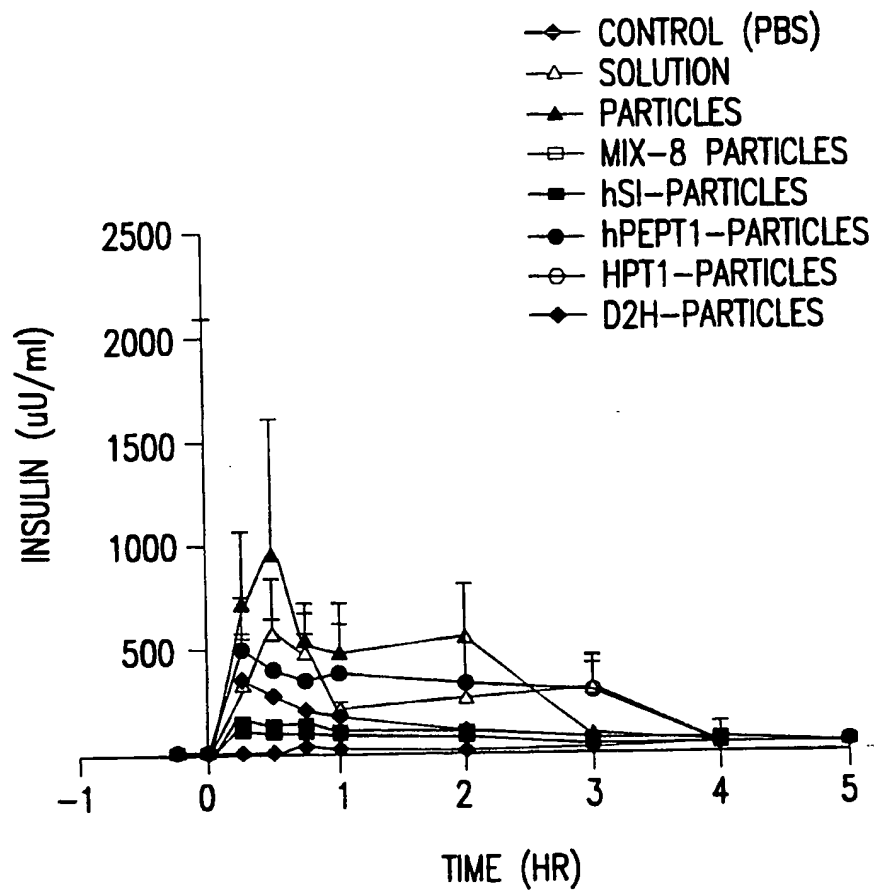


FIG. 17B

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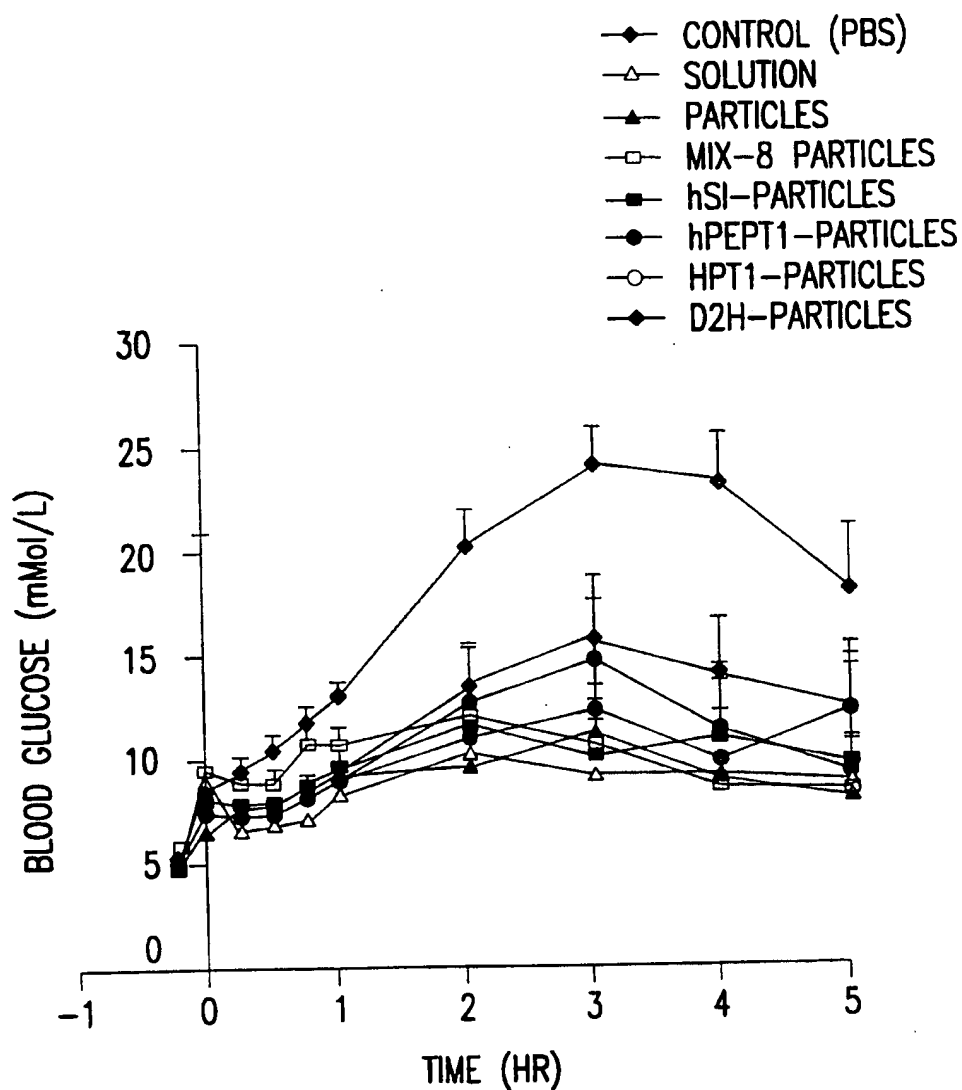


FIG. 17A

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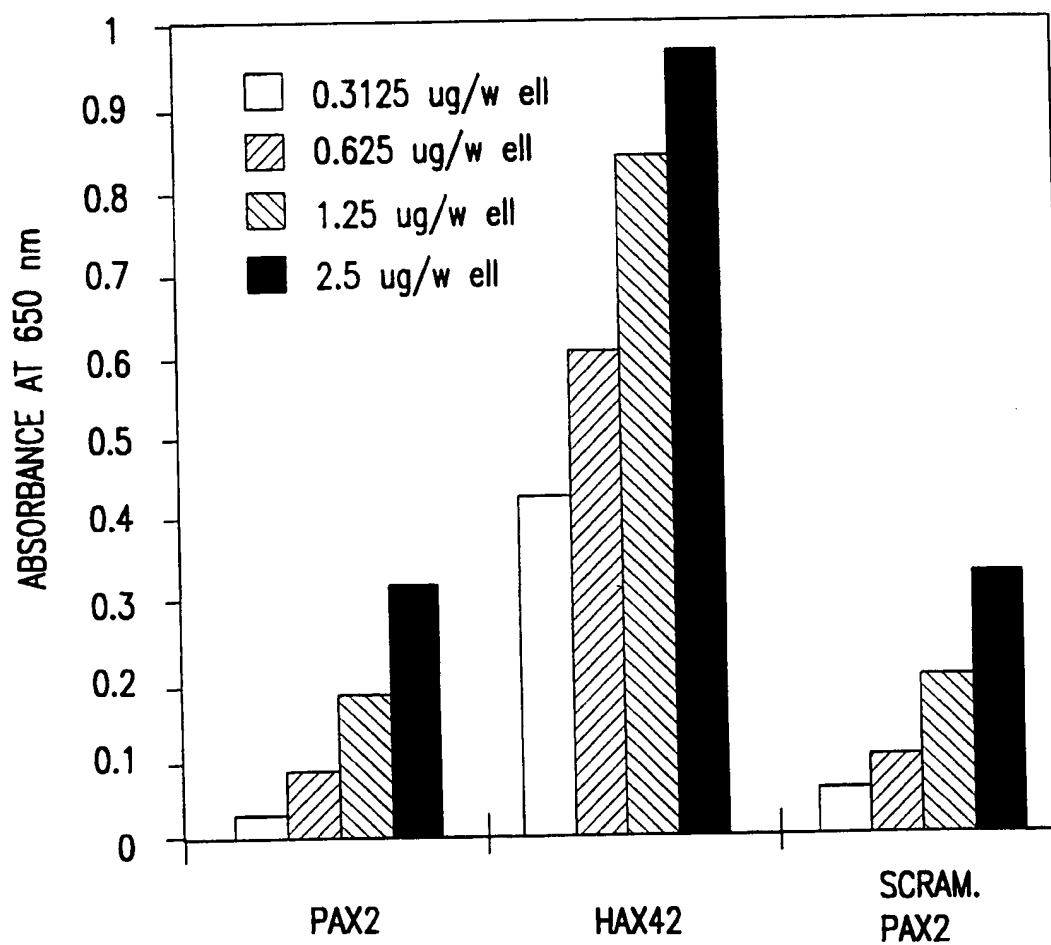


FIG. 16B

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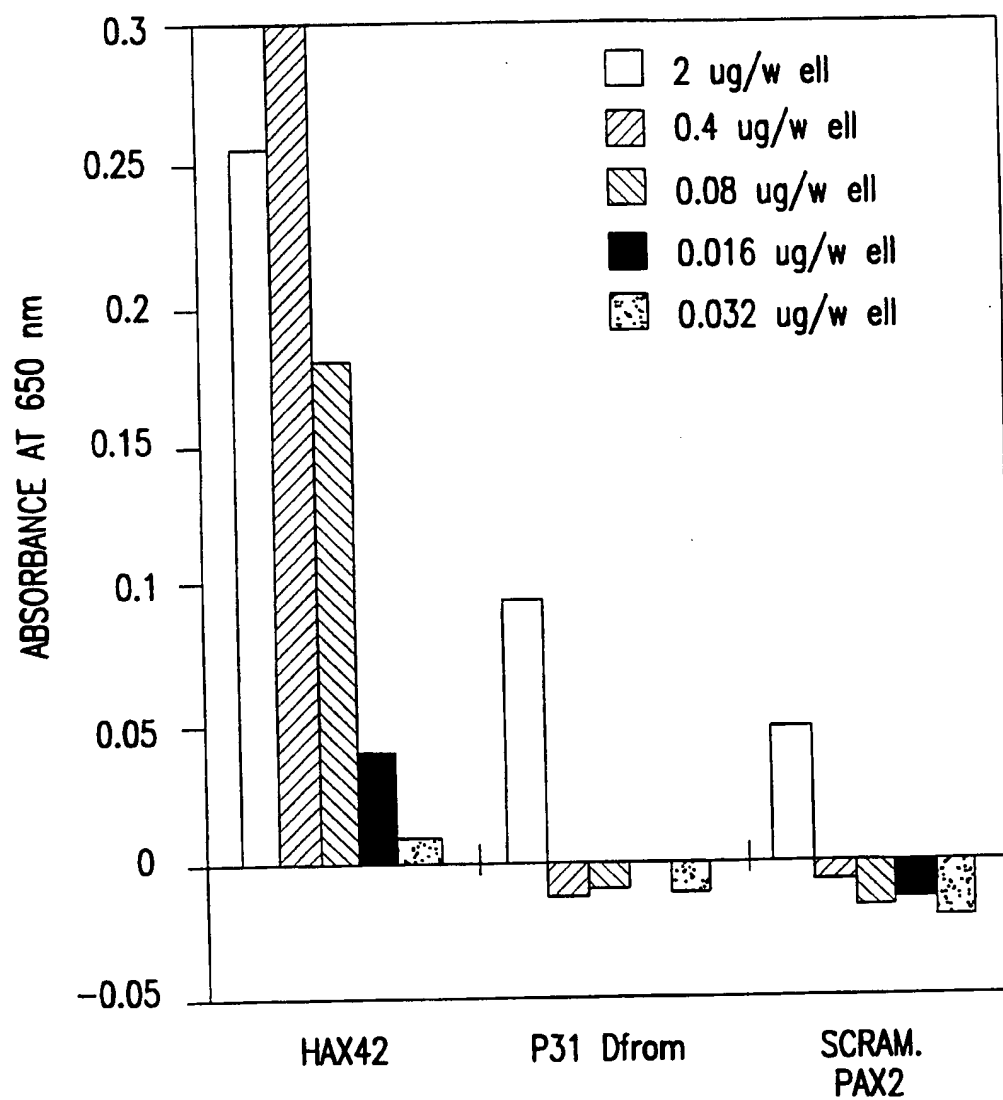


FIG.16A

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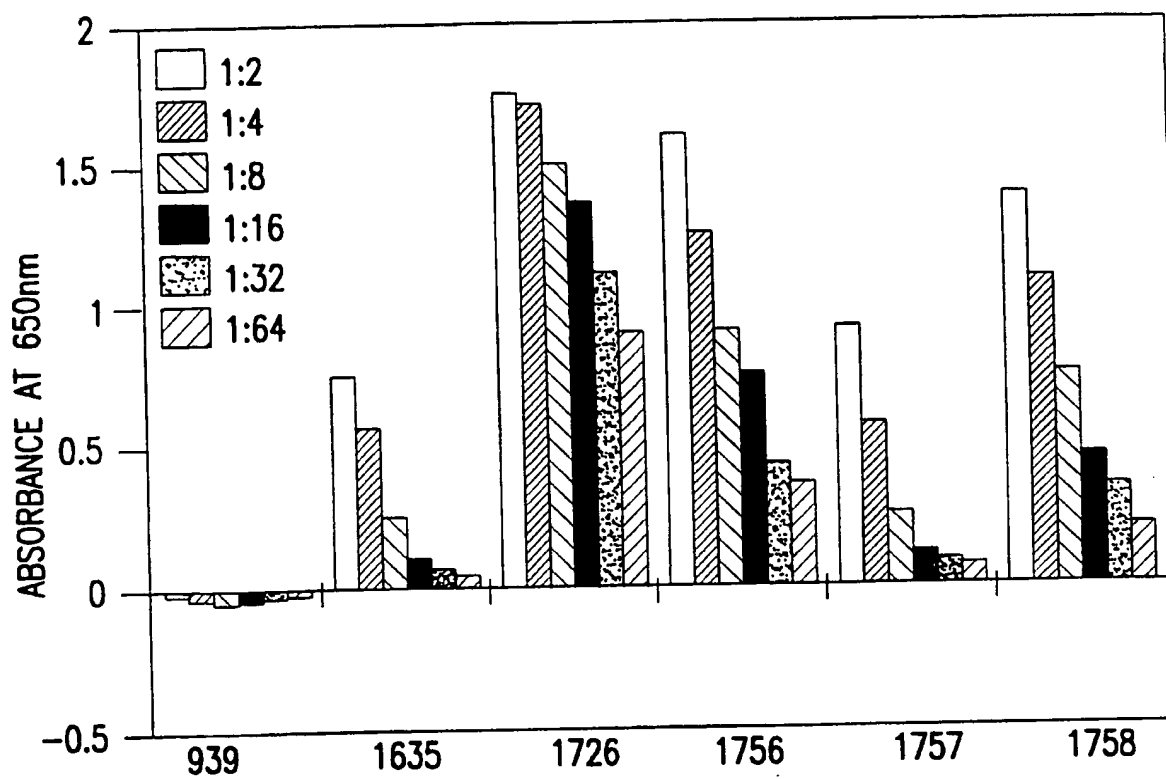


FIG. 15B

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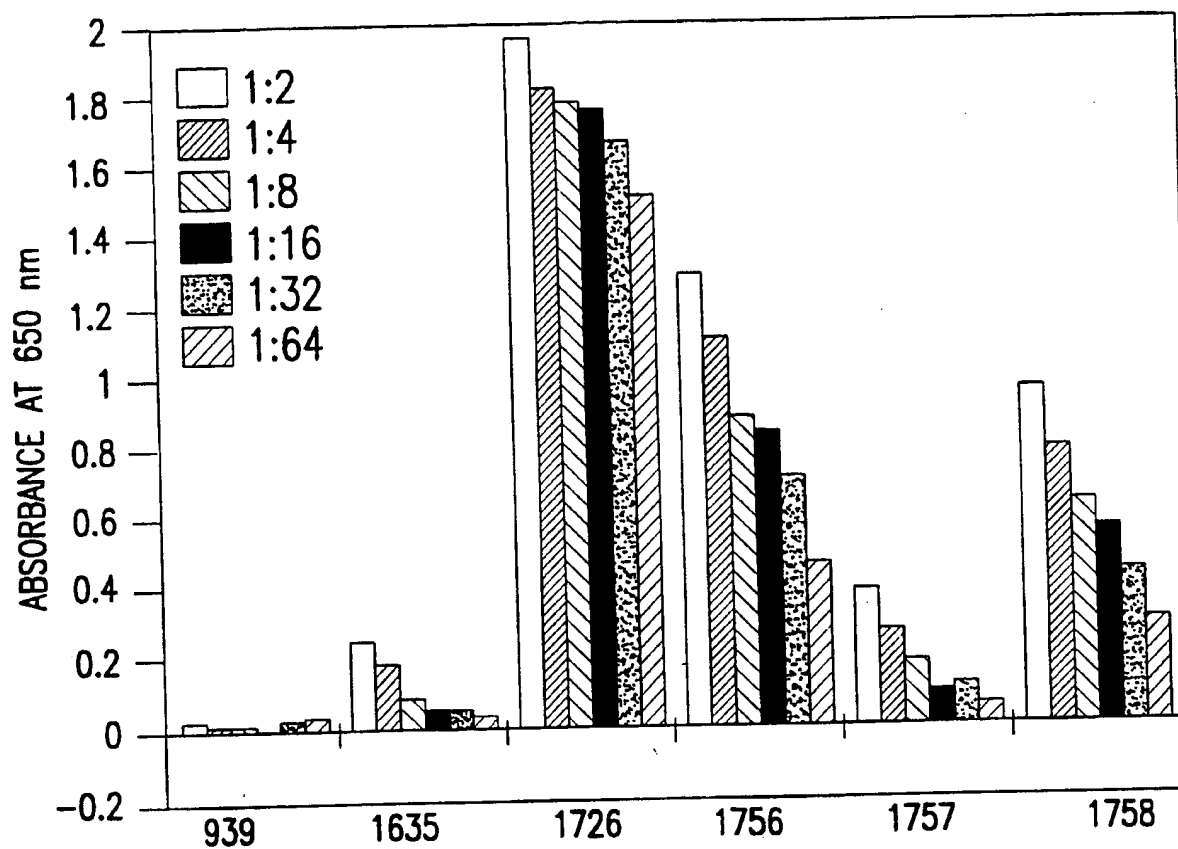


FIG. 15A

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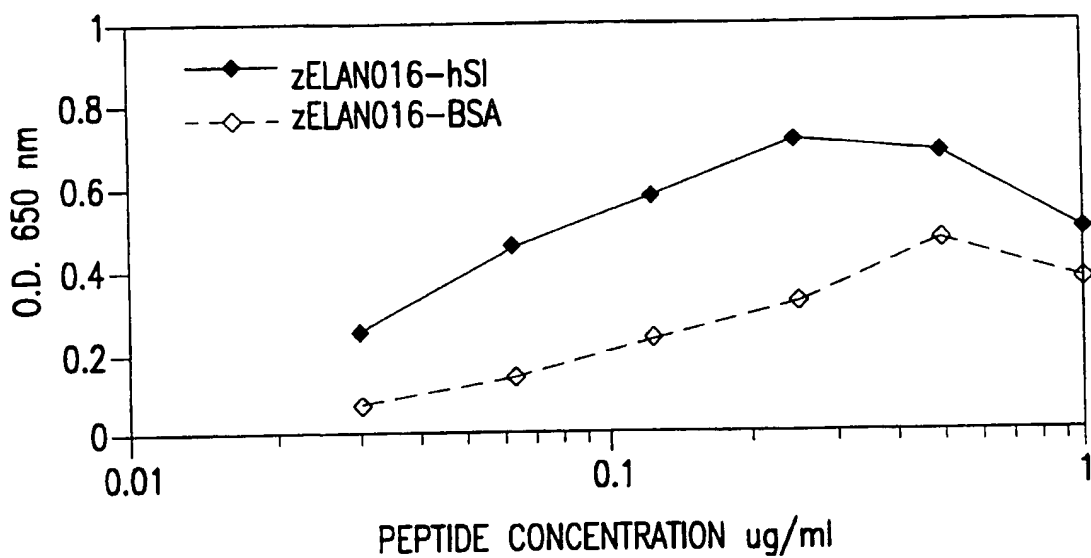


FIG. 14A

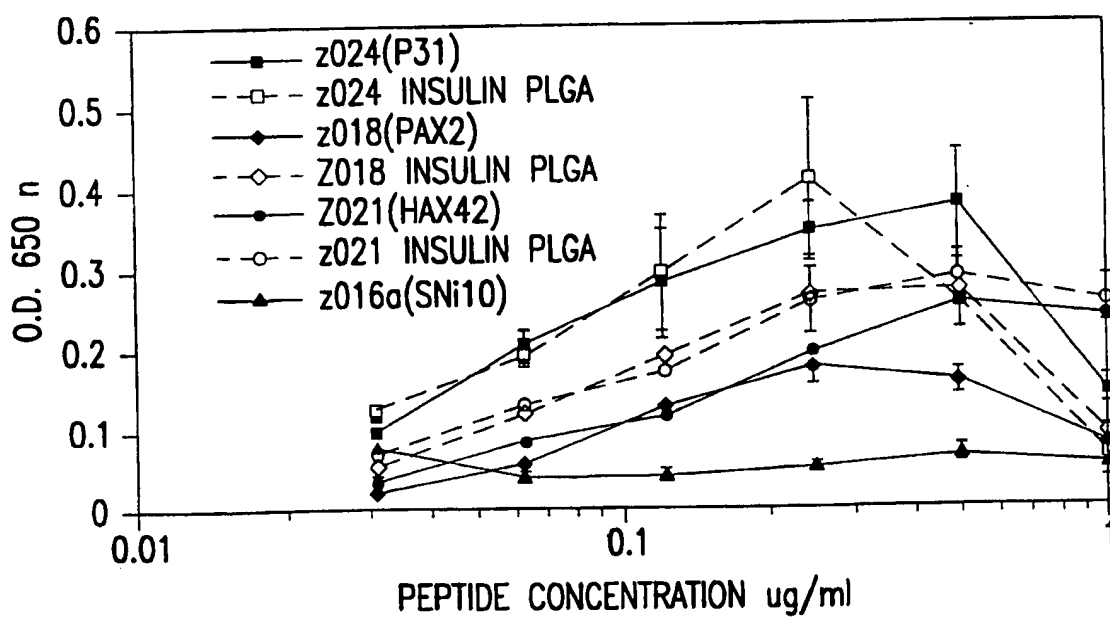


FIG. 14B

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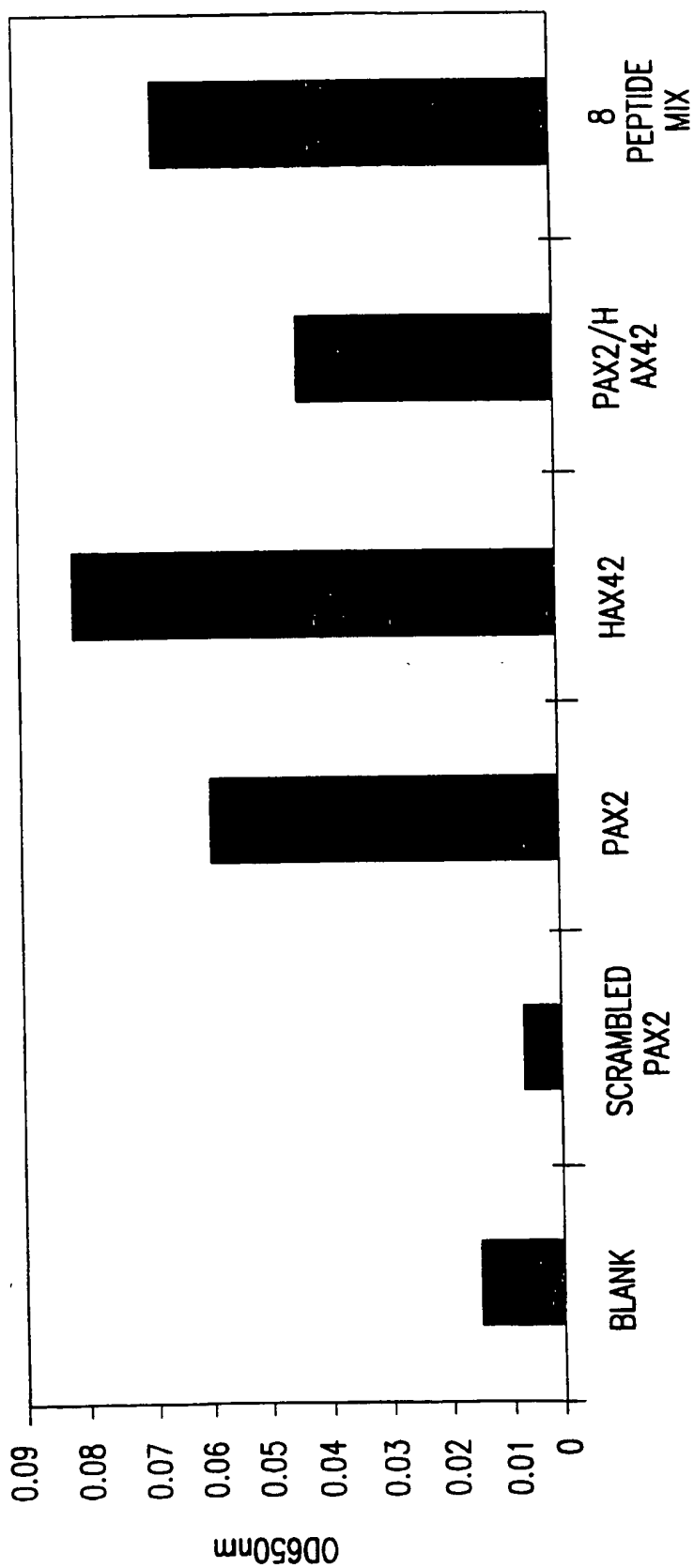


FIG.13B

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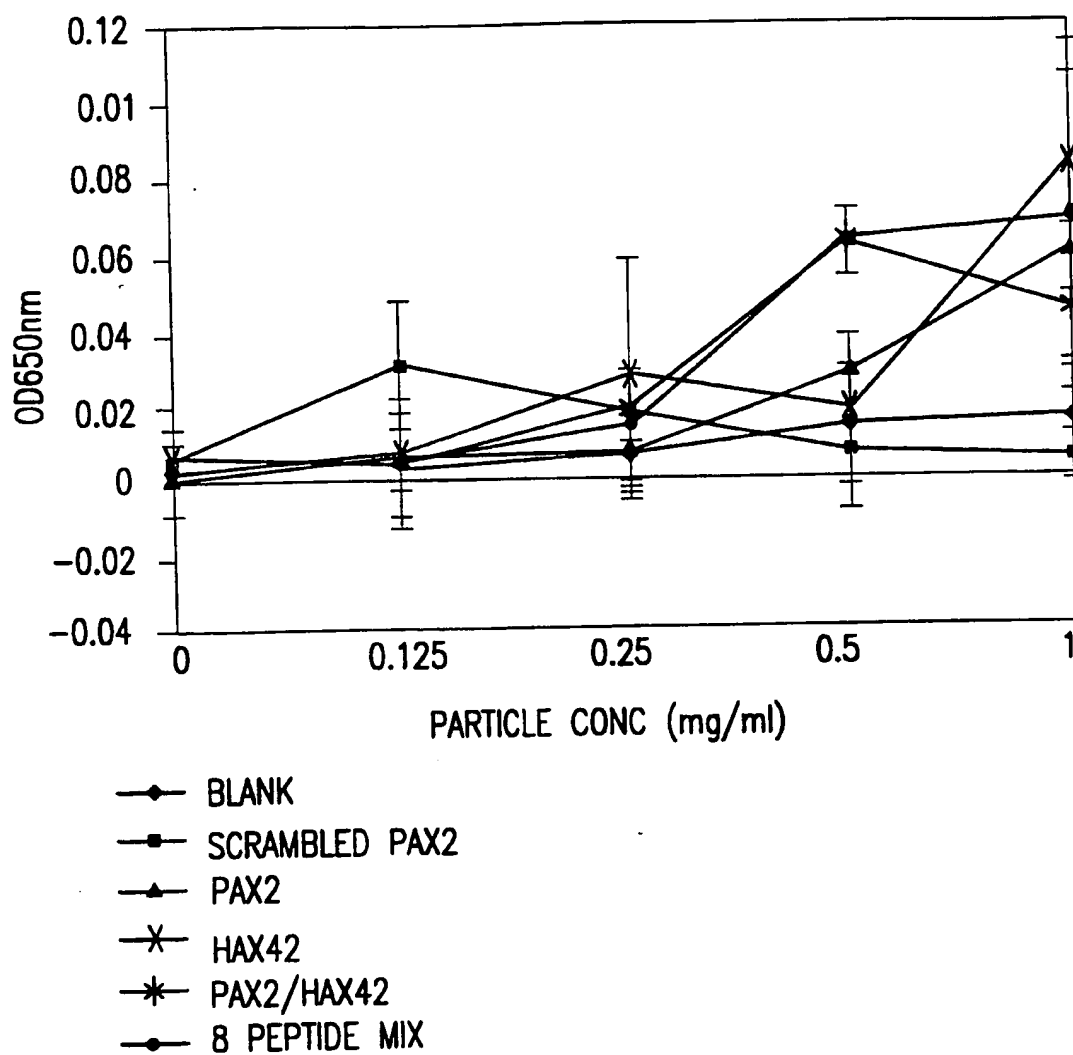


FIG.13A

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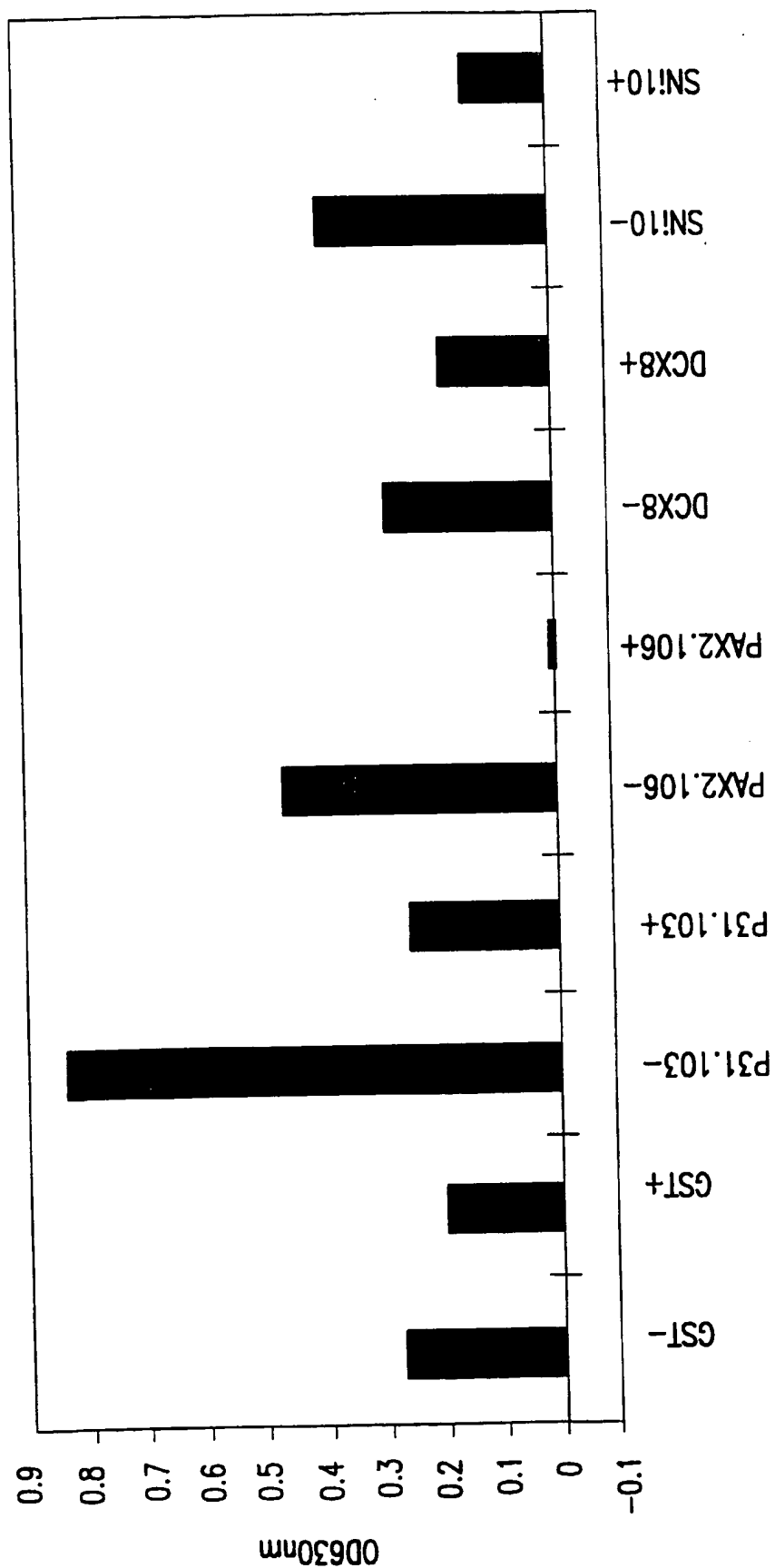


FIG.12

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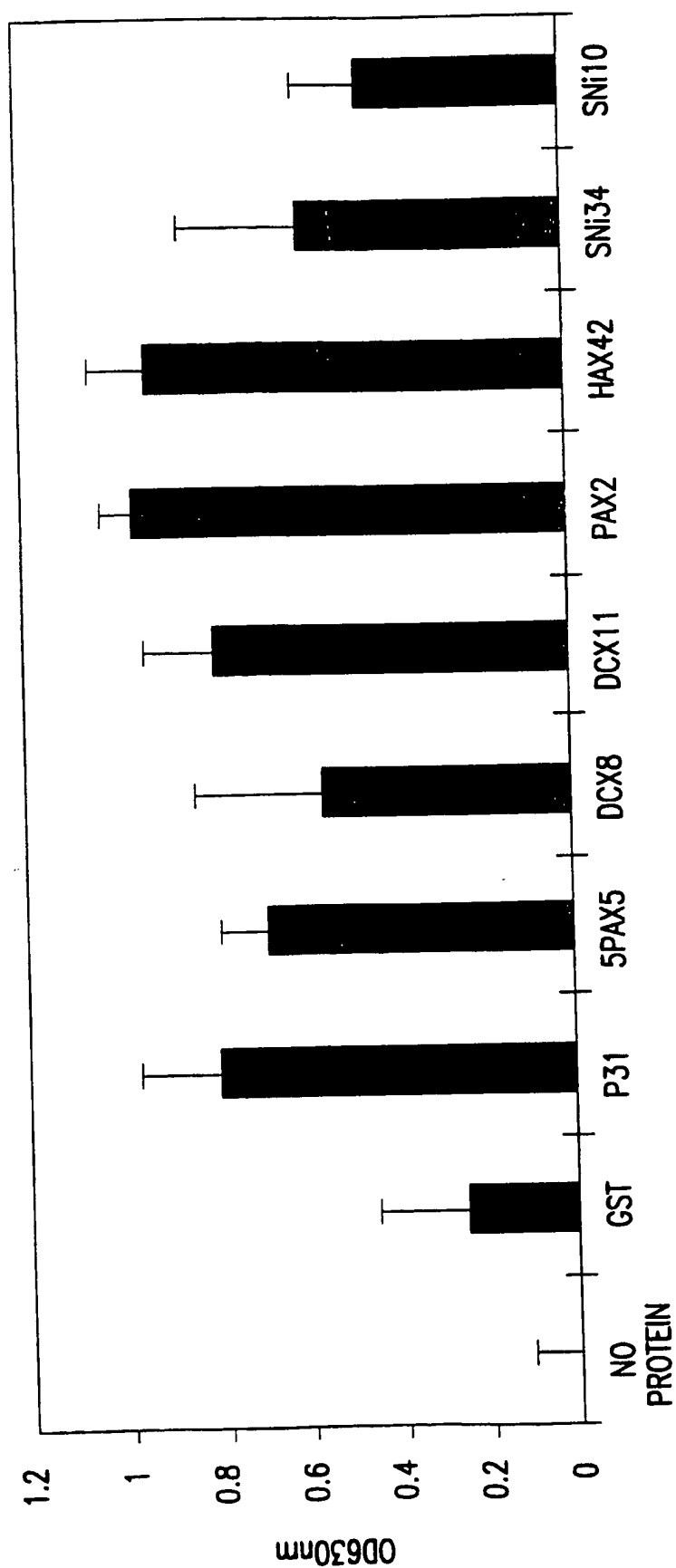


FIG.11B

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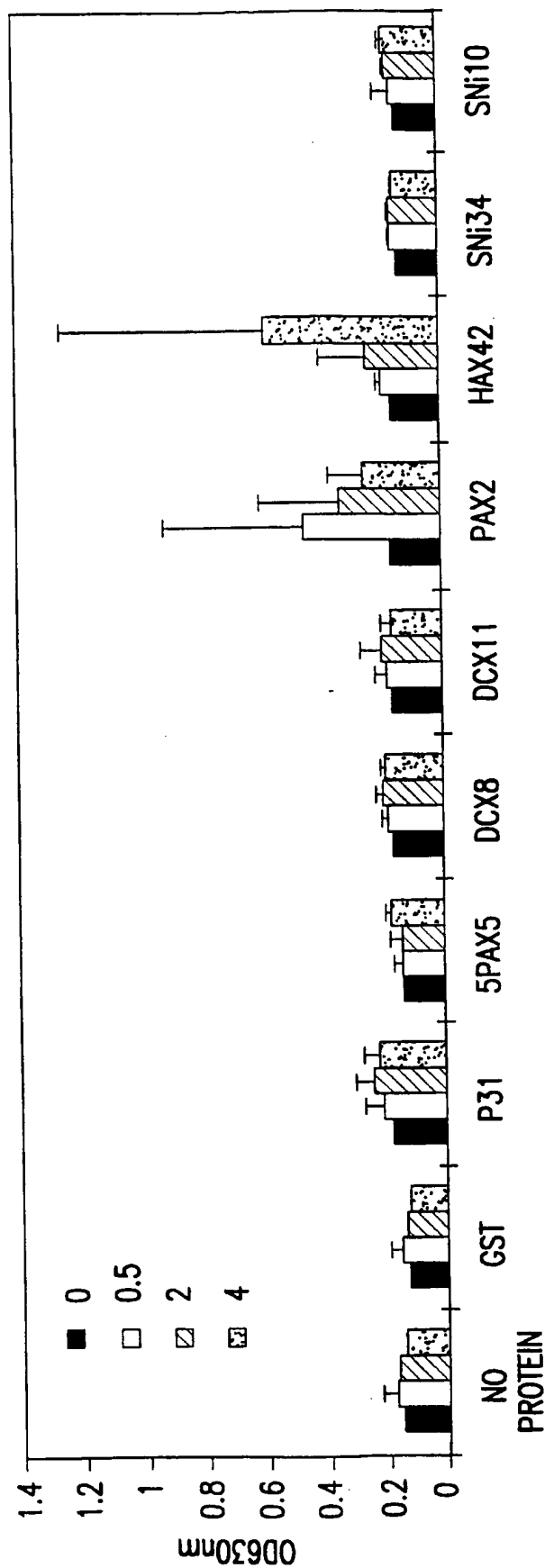


FIG.11A

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SN: 10	Peptide Name	Sequence	pI	IC ₅₀	GST/C2BBel
	ELAN016 (SNi10)	1 RVGQCTSDVRRPWARSCAHQGGAGTRNSHGCIITRPLRQASAH 40	10	0.22	++
116		RVGQCTSDVRRPWARSCA	19		-
117		VRRPWARSCAHQGGAGTRNS			+
118		GTRNSHGCIITRPLRQASAH			+/-
Z17		ZRVGQCTSDVRRPWARSCAH	8.66	3.6	
Z16C23		ZCGAGTRNSHGCIITRPLRQASAH	9.03	0.7	
Z36		ZVRRPWARSCAHQGGAGTRNS	11.62	0.27	
Z37		ZCTDSDVRRPWARSC	8.01	3	
	Peptide Name	Sequence	pI	IC ₅₀	GST/C2BBel
	ELAN021 (HAX42)	1 SDHALGTNLRSDNAKEPGDYNCCGNGNSTGRKVFNRRRPSAIP 40	11	5.5	++
	ELAN018 (PAX2)	STPPSREAYSRPYSDSDTNAKHSSHNRLRTRSPNG	10.88	0.23	+++
Z26		ZSEANLDGRKSRYSPPRRNSTTRPTSPNSVHARYPSTDHD	10.88	<0.2	
Z38		ZSRANTDGRKSRYSPPRRNSTTEPRLSPNSVHARYPSTDHD	10.88	<0.2	
Z34 (PAX2 14mer)		ZSSHNRRLRTRSPN	12.7	0.33	

FIG.10C

Peptide Name	Sequence	pI	IC ₅₀	GST/C2BBel
ELANO18(PAX2)	1 10 20 30 40 STPPSREAYSRPYSDSDTNAKHSSHNRLRTRSRPNG STPPSREAYSRPYSDSDSD SRPYSDSDSDTNAKHSSHN TNAKHSSHNRLRTRSRPN TNAKHSSHN TNAKHSSHN SSHNRLRTR RRLRTRSRPN	10.88 0.6-0.9. 1	+++	-
104				-
105				++
106				-
113				+/ -
114				+/ -
115				+/ -
Z32	ZTNAKHSSHNRLRTRSRPN	12.7	1.2	
Z33	ZTNAKHSSHNRLRTR	12.58 1.6		
Z34	ZSSHNRRLRTRSRPN	12.7	1.6, 1.3, 0.68, 1.5	
Z35	ZSSHNRRLRTR	12.58 0.38 - 1.8, 2.7		
Z26	ZSEANLDGRKSRYSPPRNSSTRPTSPNSVHARYPSIDHD	10.88 7-8, 3		
Z38	ZSRANTDGRKSRYSPPRNSSTEPRLSPNSVHARYPSIDHD	10.88 1.7, 0.9		
Z55	ZTNAKHSSHN		42	
Z56	ZRRLRTRSRPN		1.7	
Z57	ZRRLRTRSRP		1.9	
Z58	ZRRLRTR	3.4		
Z59	ZrrLrTrSrPN		NOT DONE	
Z73	ZASHNRRLRTR	1.5,	5.5	
Z74	ZSAHNRLRTR	6.2		
Z75	ZSSANRLRTR	1.6		
Z76	ZSSHARLRTR	1.8		
Z77	ZSSHNA RLTR	3.9,	5.2	
Z78	ZSSHNRALRTR	4.5,	4.6	
Z79	ZSSHNRRLRTR	1.4		
Z80	ZSSHNRRLATR	3.4,	5.2	
Z81	ZSSHNRRLRAR	2.2		
Z82	ZSSHNRRLRTA	3.4		
Z21 (HAX42)	ZSDHALGTNLRSDNAKEPGDYNCCGNGNSTGRKVFNRRPSAIP	11.27 0.7		

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FIG. 10B

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Peptide Name	Sequence	pI	IC ₅₀	GST/C2BBel
ELANO24(P31)	1 10 20 30 40 SARDSGPAEDGSRVRLNGVENANTRKSSRSNPRGRRHHPG	11.88	0.5-2.2	+++
101	SARDSGPAEDGSRVRLNG			
102	DGSRVRLNGVENANTRKSSR			
103	ENANTRKSSRSNPRGRRHHP			++
110	ENANTRKSSR			
111	RKSSRSNPRG			
112	SNPRGRKRP			
119	TRKSSRSNPRG			
Z28	ZENANTRKSSRSNPRGRRHHPG	12.28	0.5-1.7	
Z29	ZTRKSSRSNPRG	12.40	5.5-15	
Z30	ZENANTRKSSRSNPRG	11.81	> 50	
Z31	ZTRKSSRSNPRGRRHHPG	12.70	0.6-3.2	
Z39	ZENANTRKSSR	10.89	> 50	
Z40	ZSNPRGRRHHPG	12.40	5.9-29	
Z41	ZENANT	3.75	>50	
Z42	ZANTRKS	11.05	>50	
Z43	ZTRKSS	11.05	>50	
Z44	ZRKSSR	12.11	13- > 50	
Z45	ZKSSRSN	11.05	40-48	
Z46	ZSSRSNPG	10.04	>50	
Z47	ZRSNPRG	12.40	>50	
Z48	ZSNPRG	10.04	>50	
Z49	ZPRGRRH	12.40	11-20	
Z50	ZRRHPG	12.10	30	
Z51 (HepC core)	ZKSSRGN	12.40	>50	
Z52 (HepC p26664)	ZKTSERSQPRGRRHQP	12.10	9.8	
Z53	ZTrKSSrSNPrGrRHHPG		1.6	
Z54	ZTRKSSrSNPRGrRHHPG		1.6	
Z21 (HAX42)	SDHALGTNLRSDNAKEPGDYNCCGNSTGRKVFNRRRPSAIP	11.27	1.7	

FIG.10A

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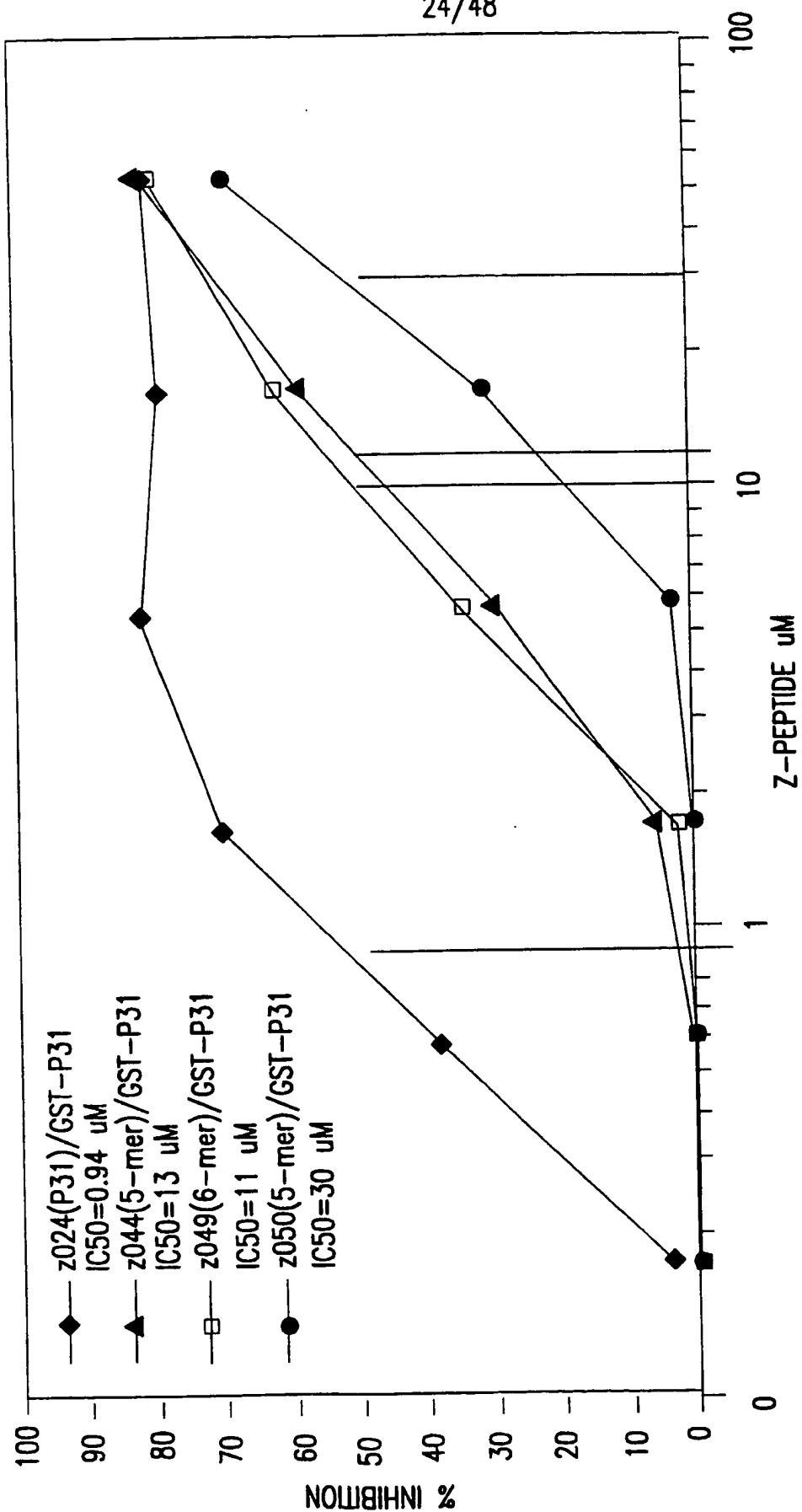


FIG.9B

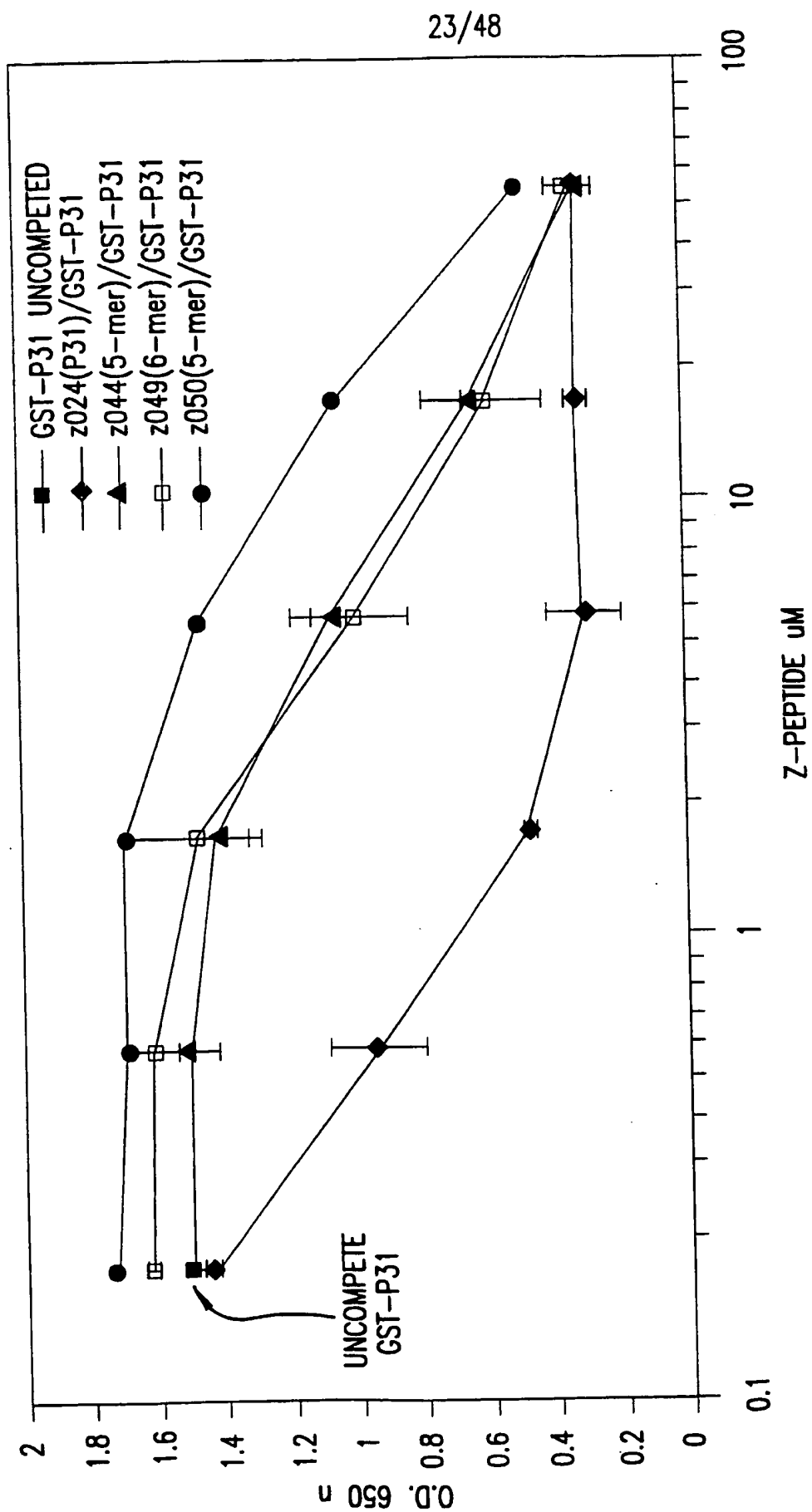


FIG.9A

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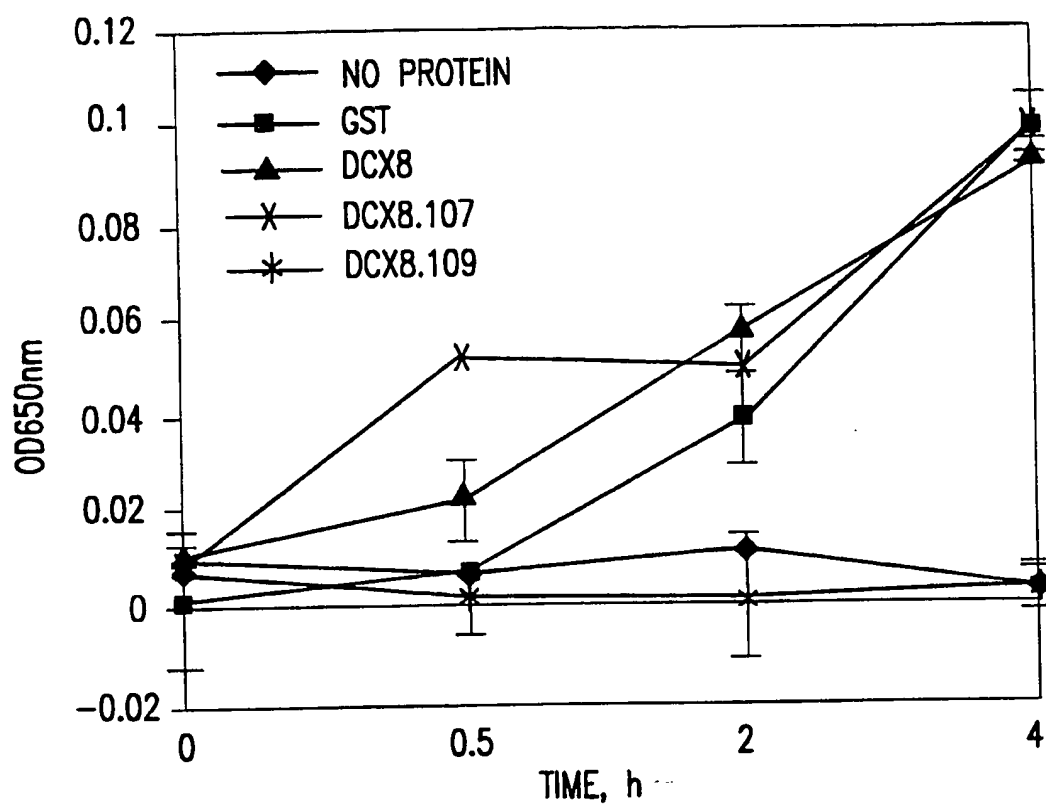


FIG.8C

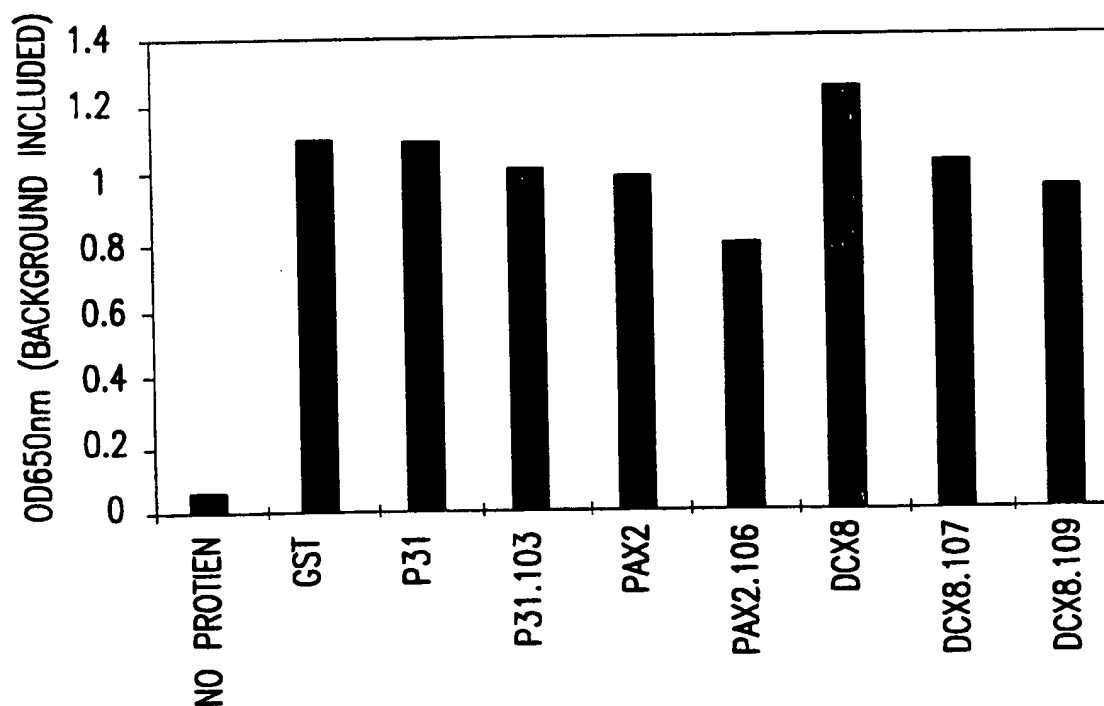


FIG.8D

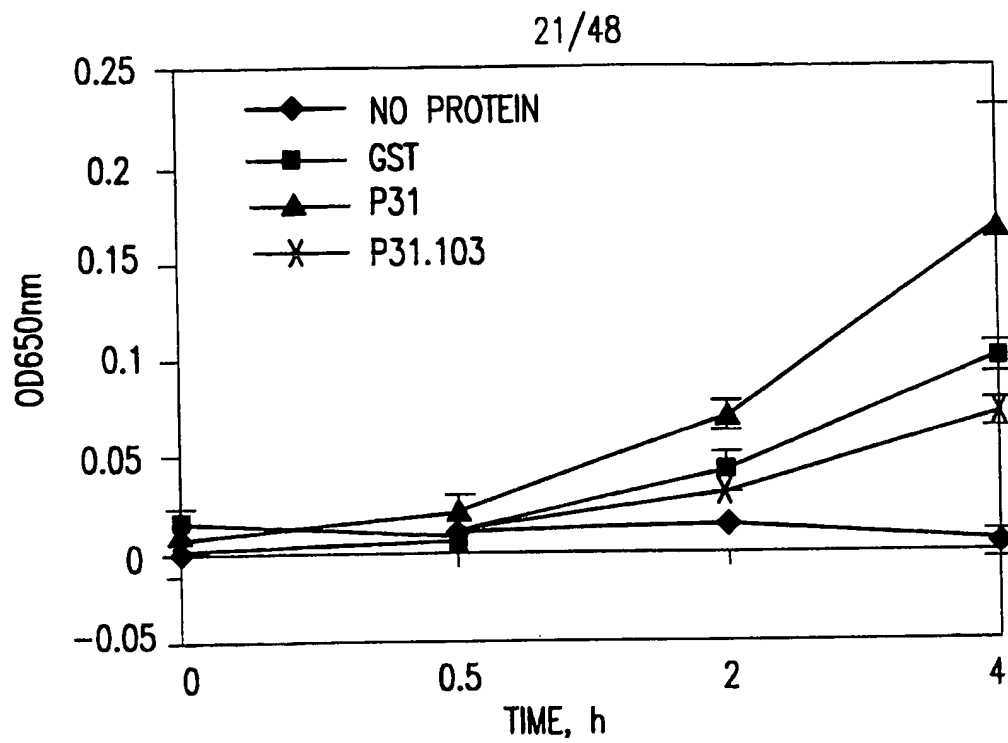


FIG. 8A

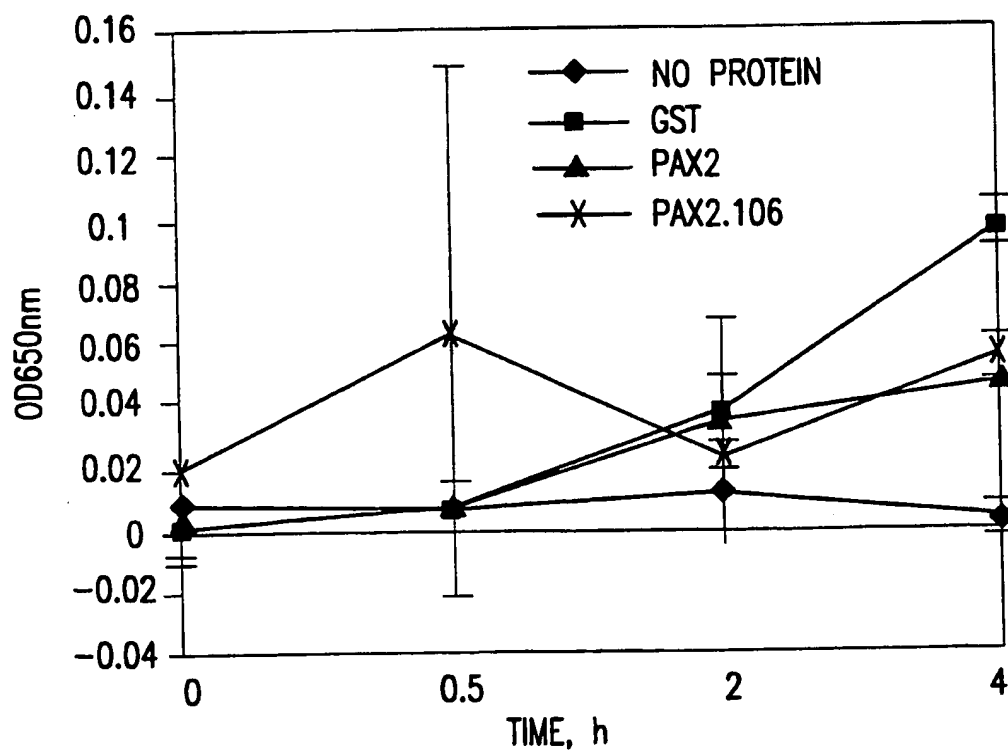


FIG. 8B

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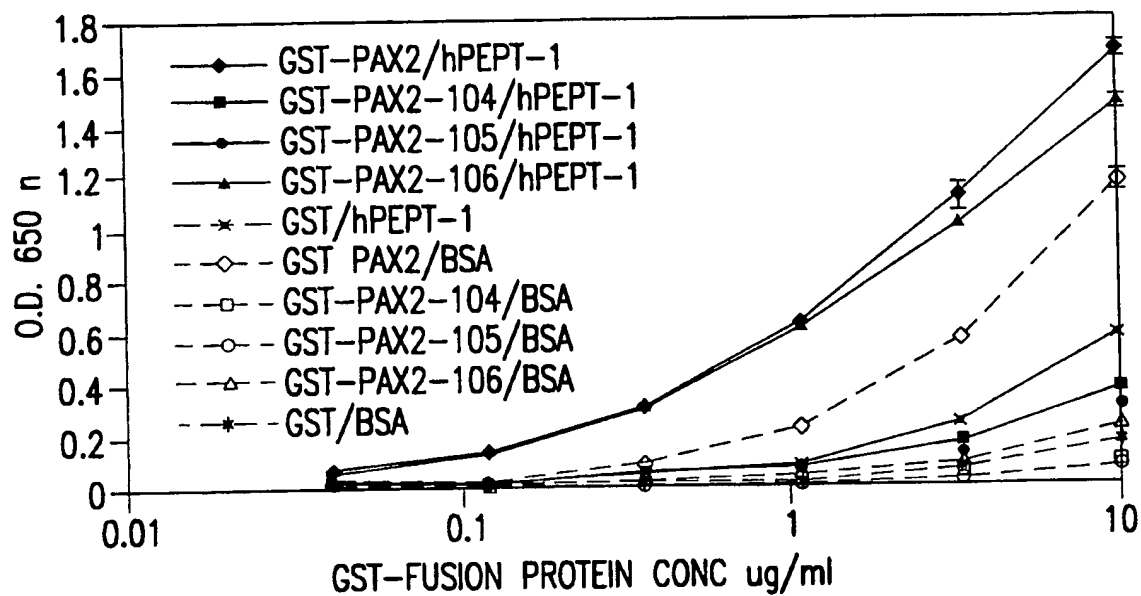


FIG. 7L

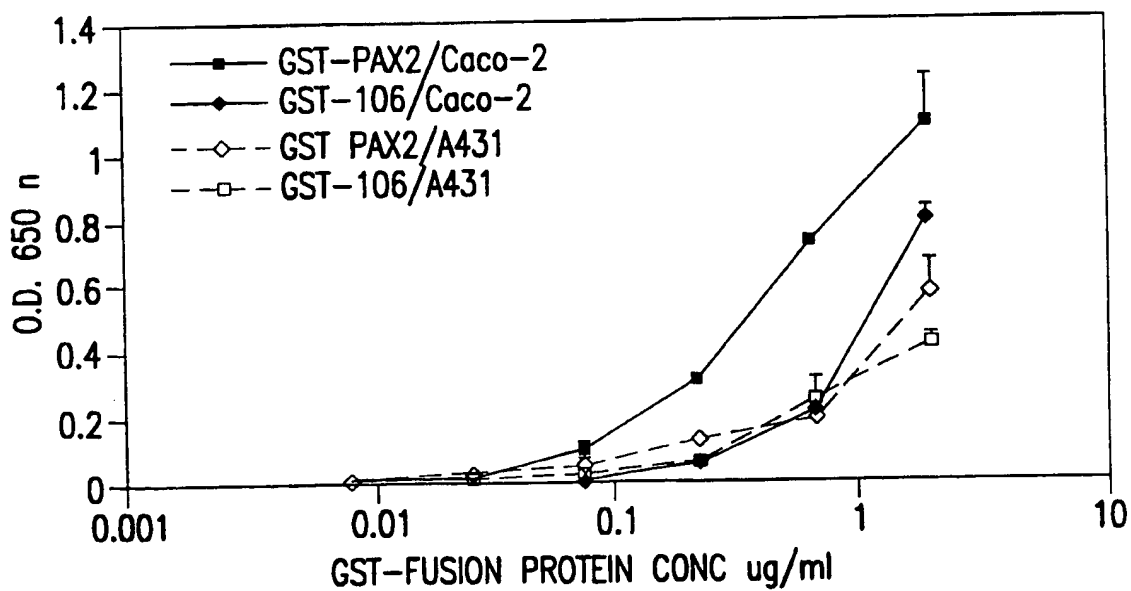


FIG. 7M

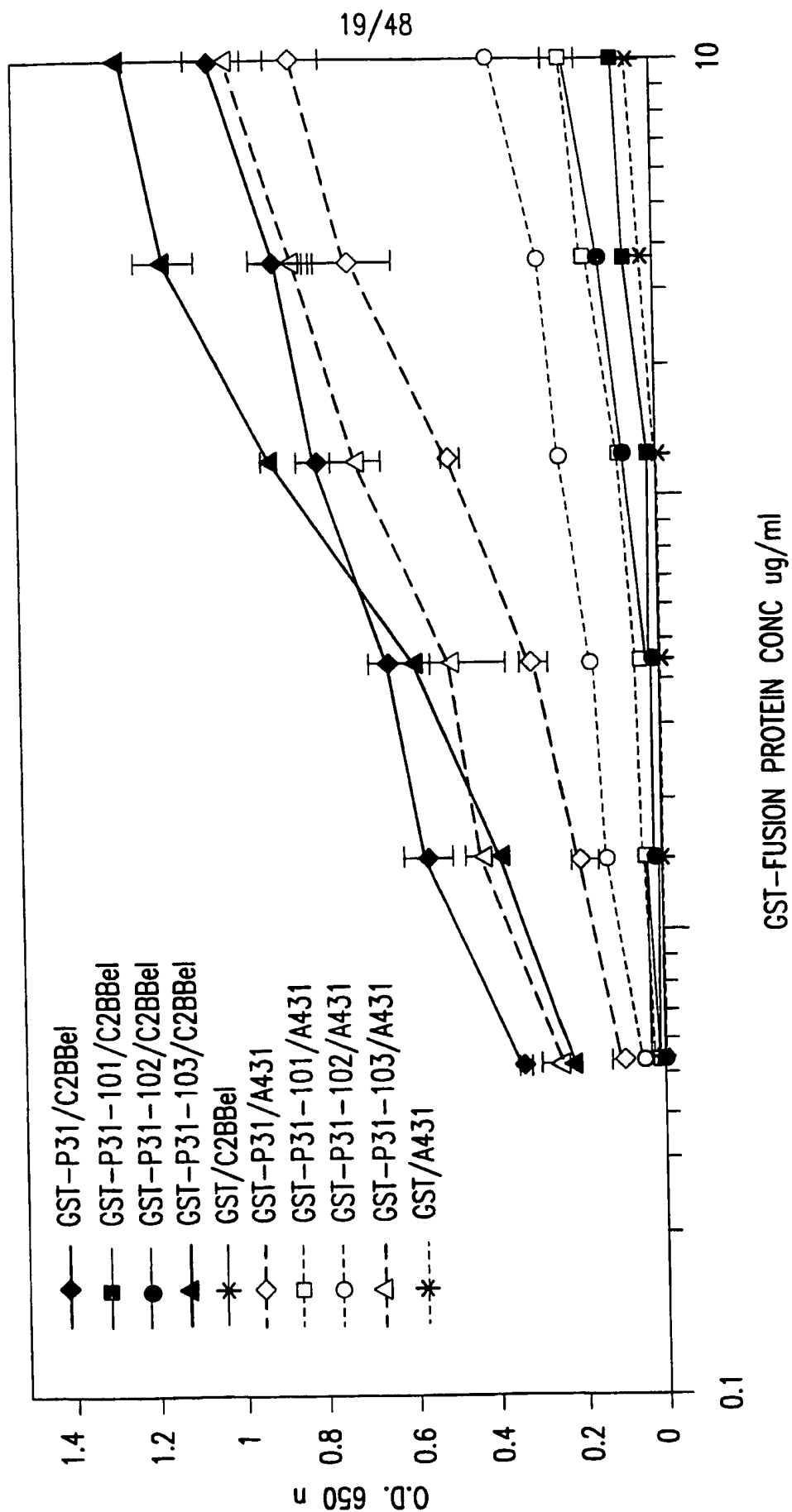


FIG. 7K

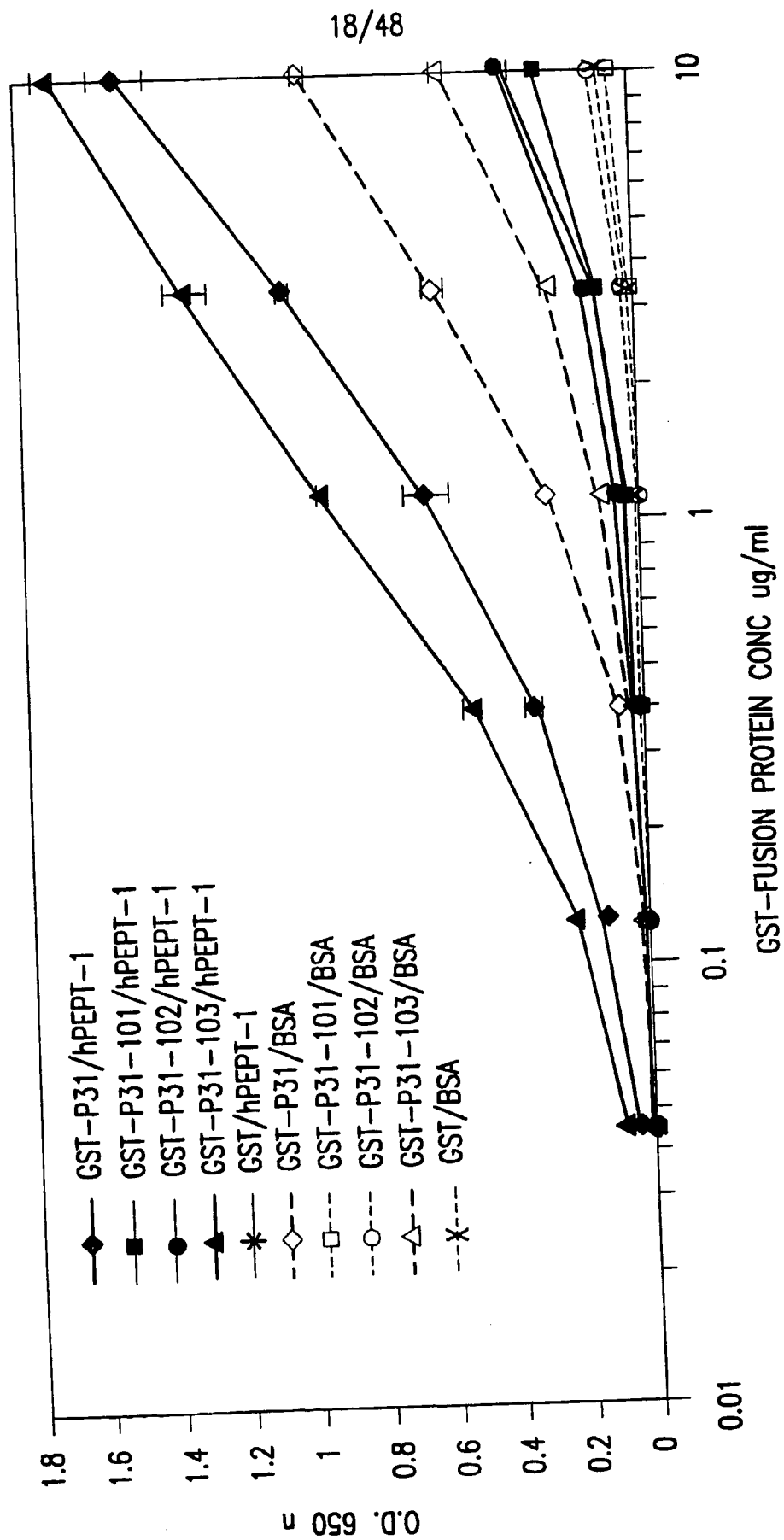


FIG. 7J

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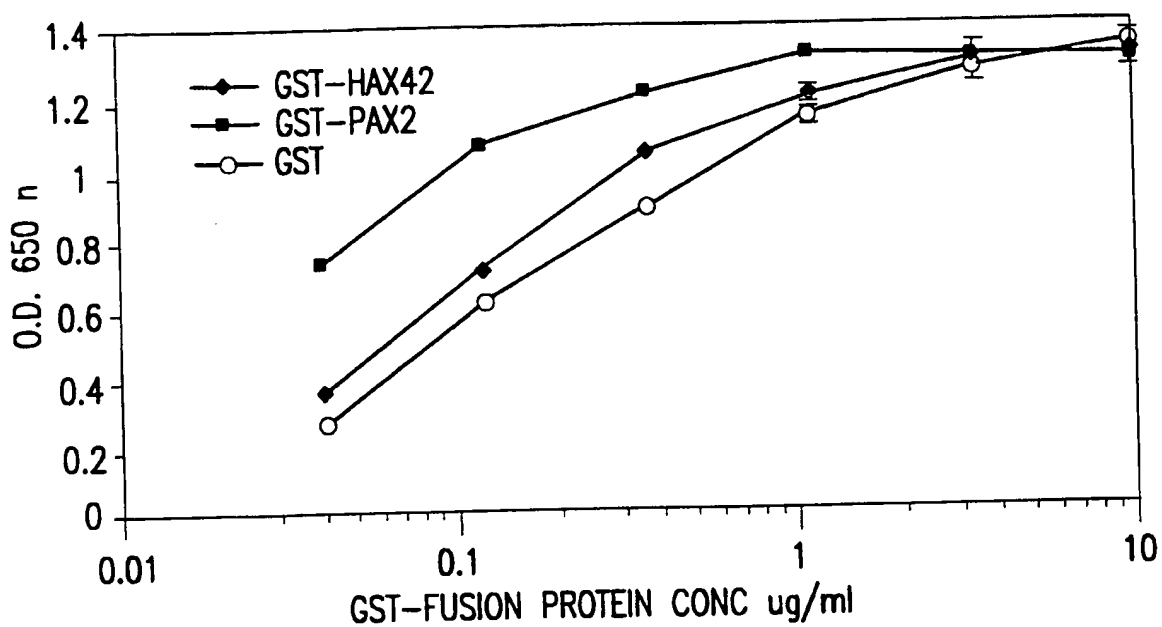


FIG.7H

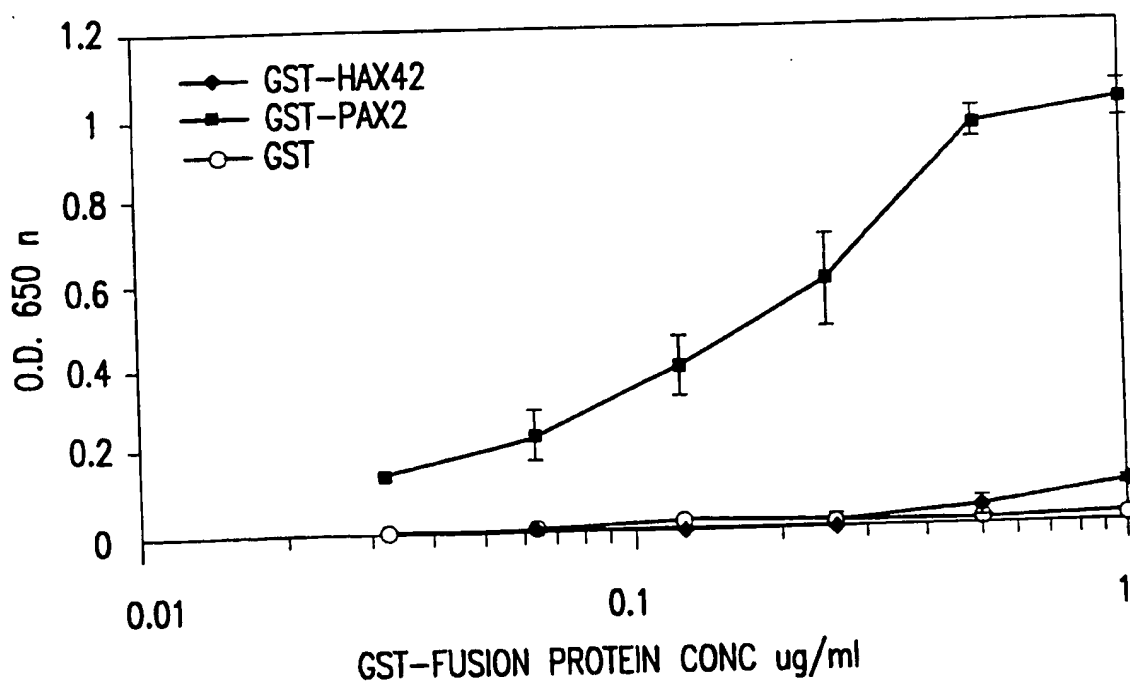


FIG.7I

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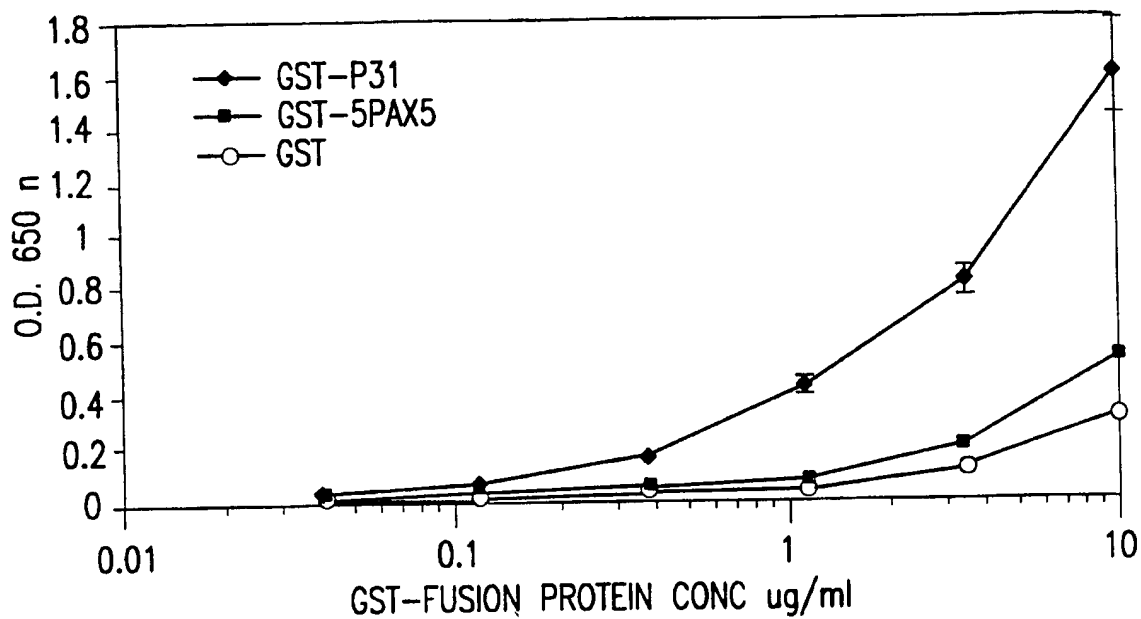


FIG. 7F

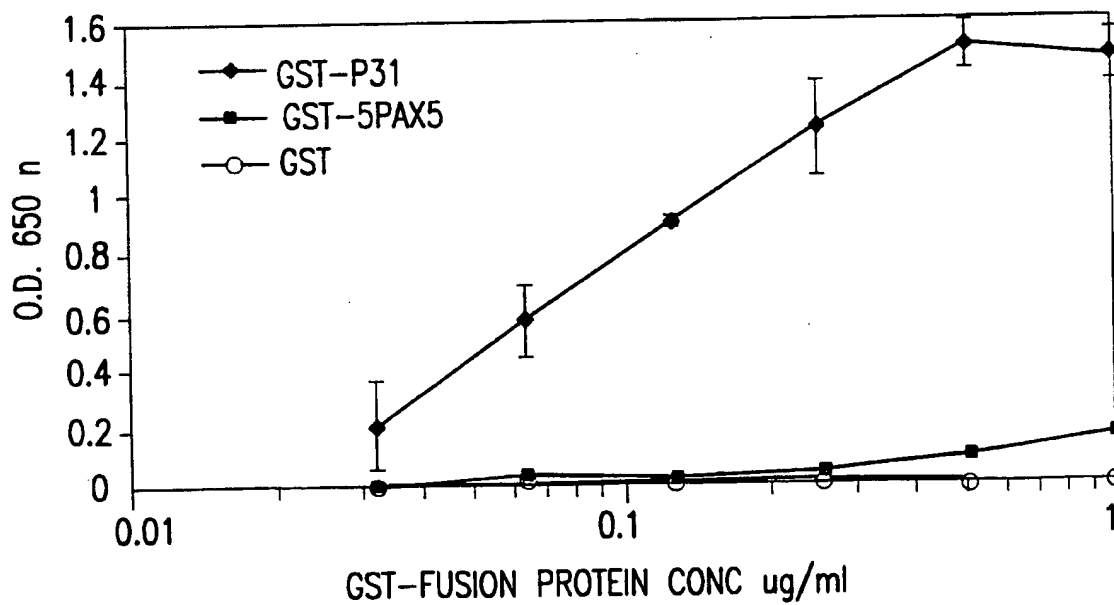


FIG. 7G

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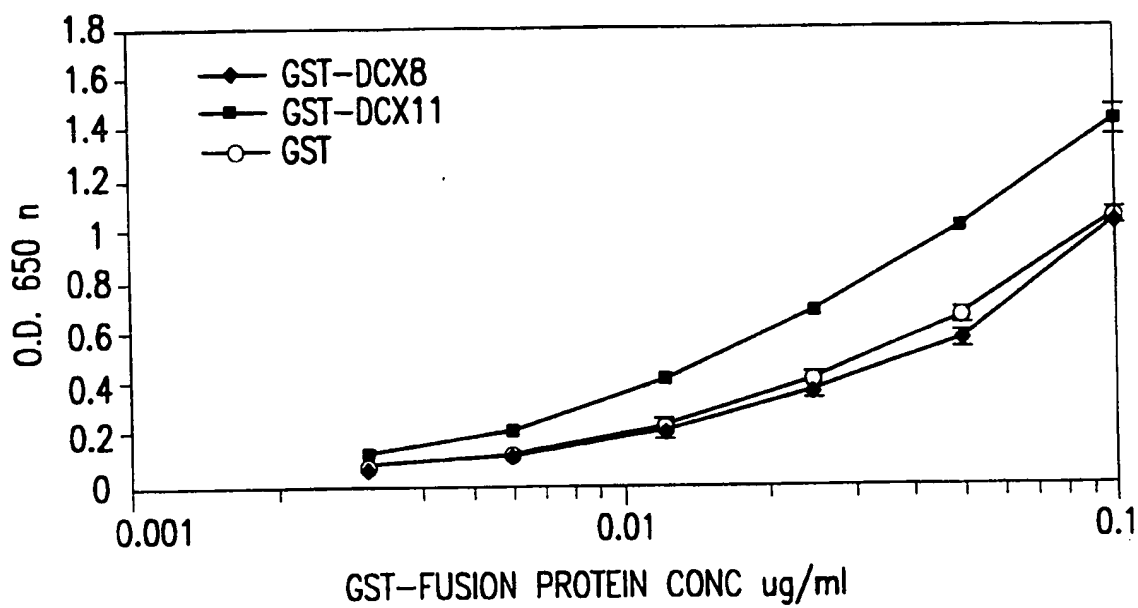


FIG. 7D

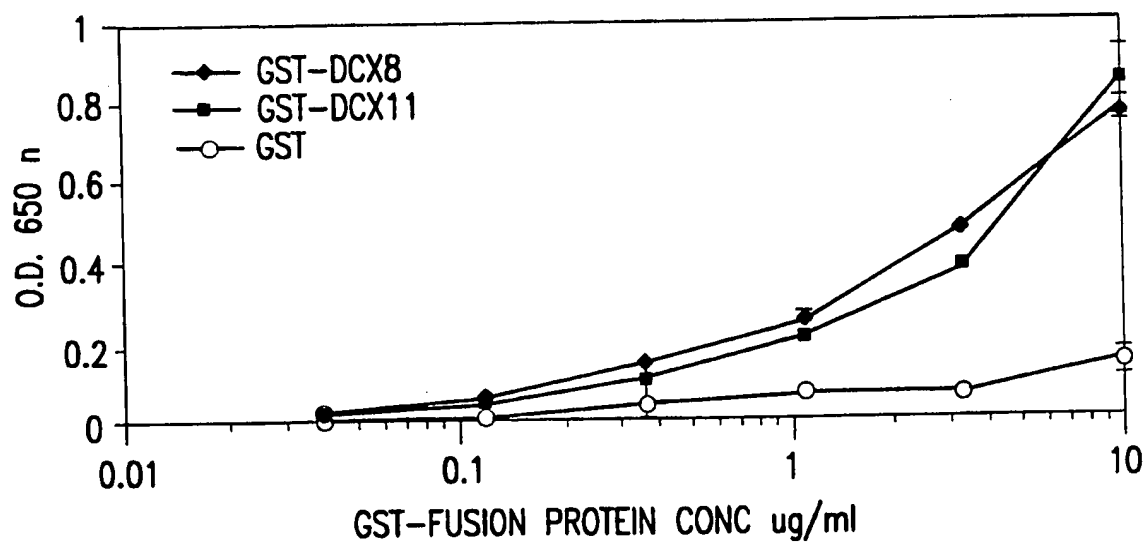


FIG. 7E

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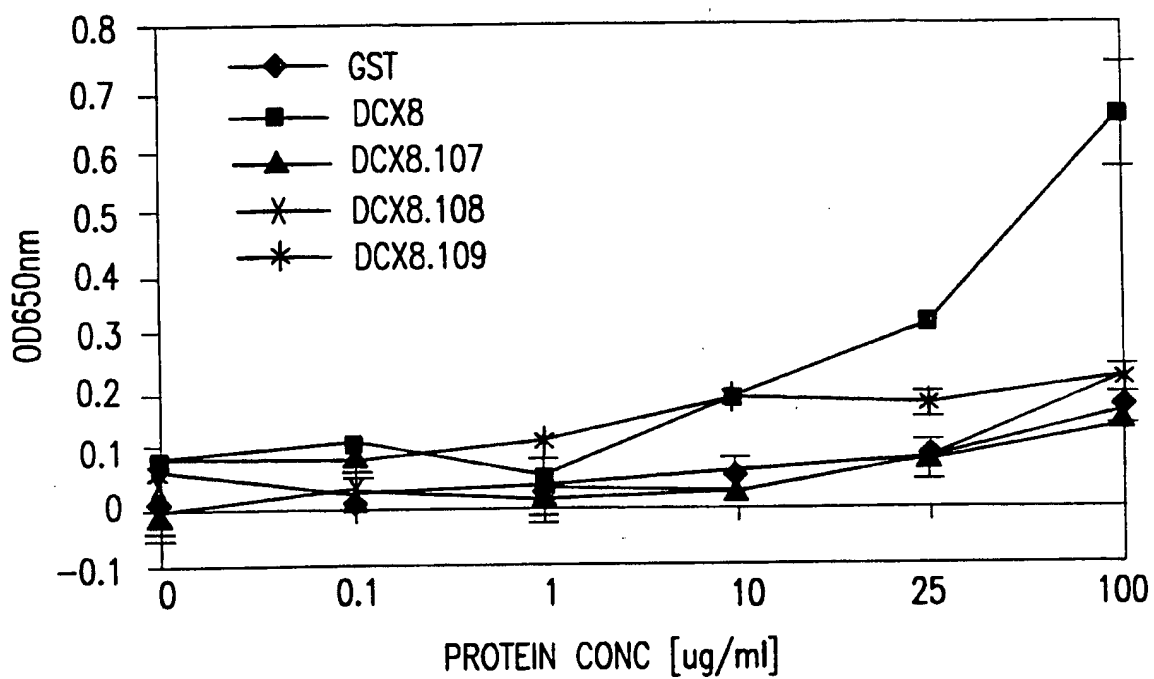


FIG. 7C

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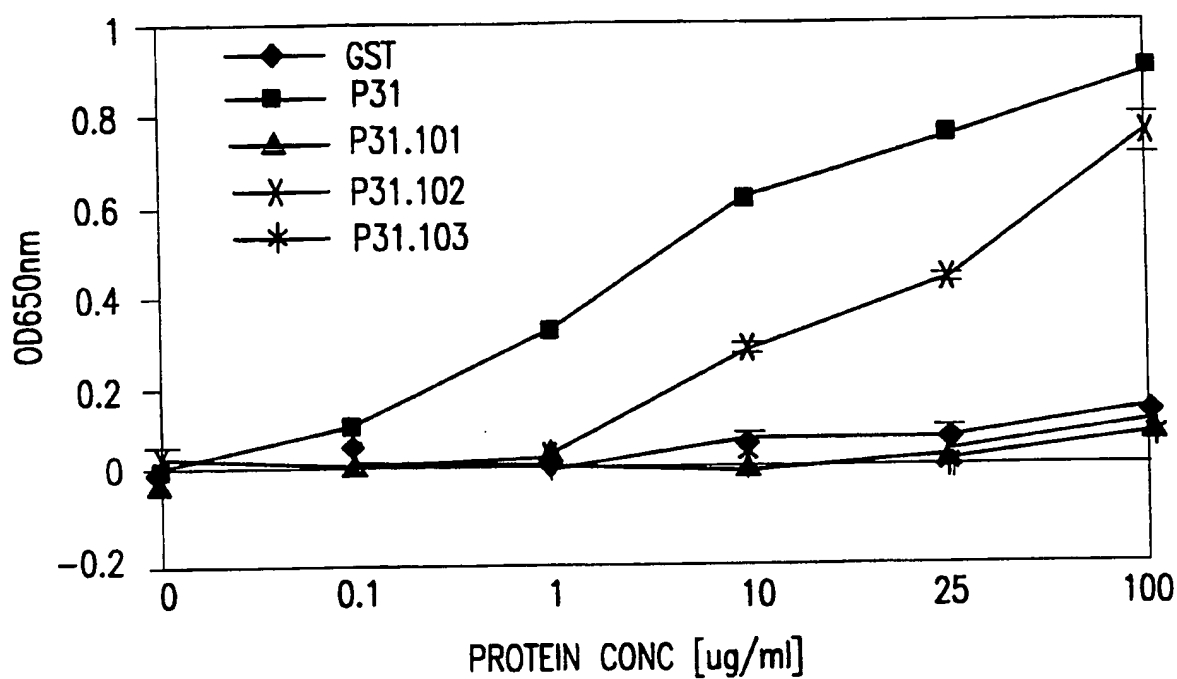


FIG. 7A

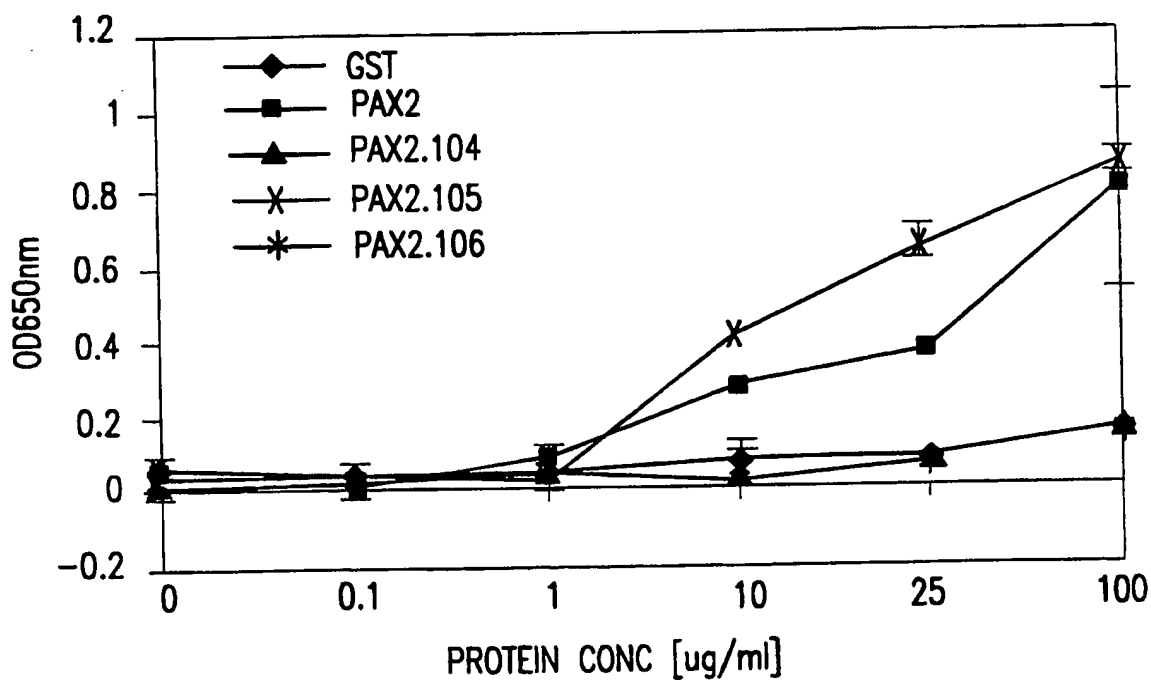


FIG. 7B

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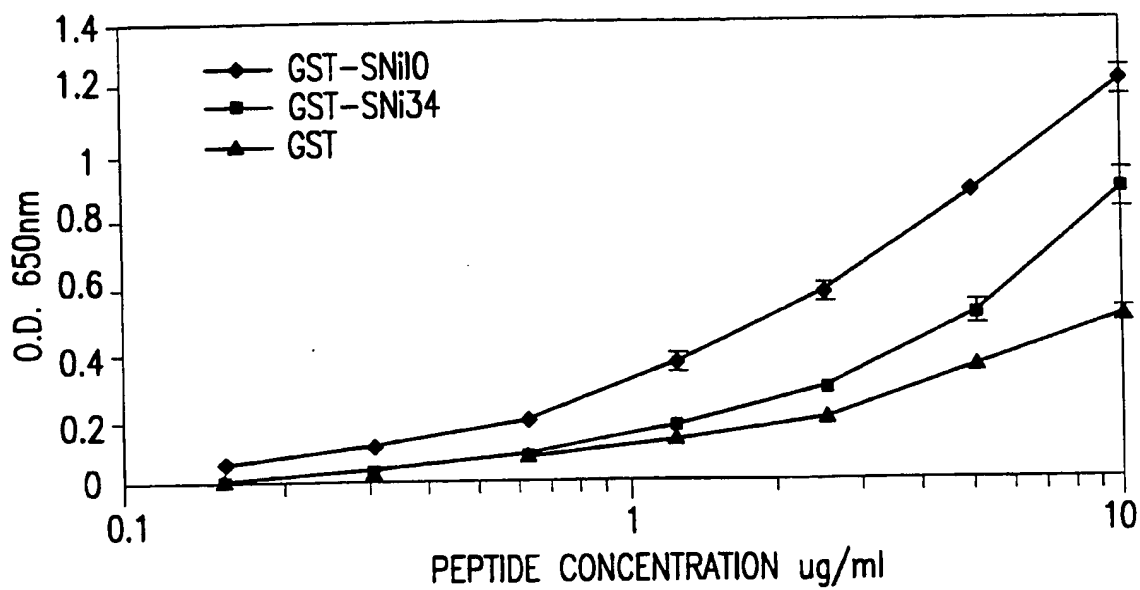


FIG.6A

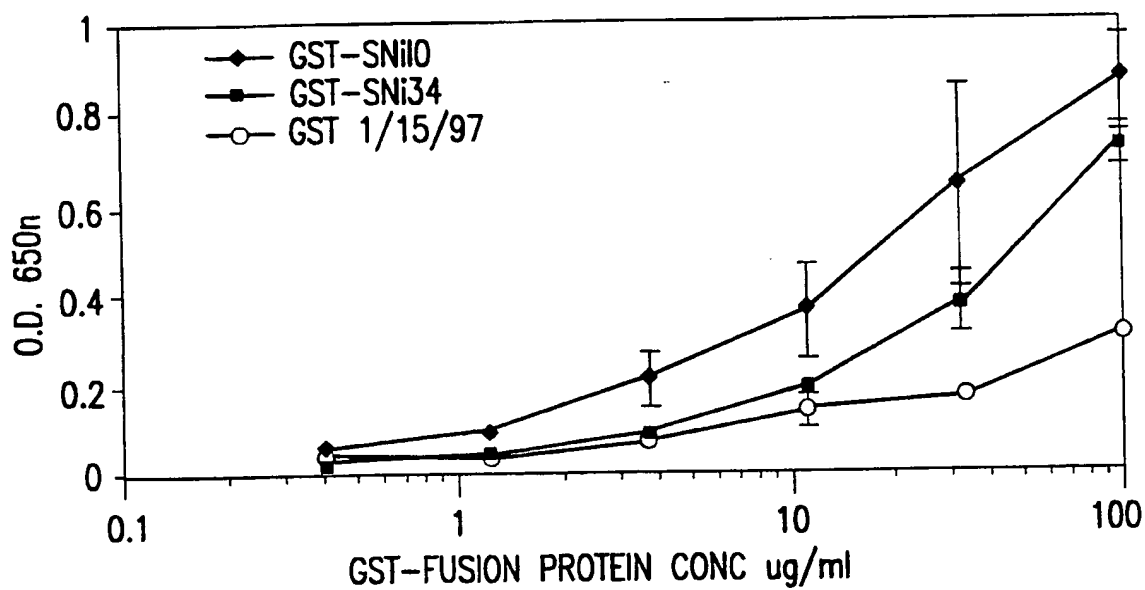


FIG.6B

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P31	1	10	20	30	Clone #
	SARDSGPAEDGSRAVRLNGVENANTRKSSRSNPRGRRHP				
			ENANTRKSSRSNPRGRRHP		103
			ENANTRKSSR		110
			TRKSSRSNPRG		119
			RKSSRSNPRG		111
			SNPRGRRHP		112
Pax2	1	10	20	30	Clone #
	STPPSREAYSRPYSVDSDDTNAKHSSHNRRLRTRSRPN				
			TNAKHSSHNRRLRTRSRPN		106
			TNAKHSSH		113
			SSHNRRLRTR		114
			RRLRTRSRPN		115
SNi10	1	10	20	30	Clone#
	RVGQCTDSDVRRPWARSCAHQCGAGTRNSHGCITRPLRQASAH				
	RVGQCTDSDVRRPWARSCA				116
		VRRPWARSCAHQCGAGTRNS			117
			GTRNSHGCITRPLRQASAH		118

FIG.5C

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P31	1	10	20	30	Clone #
	SARDSGPAEDGSRVRLNGVENANTRKSSRSNPRGRRHP				101
	SARDSGPAEDGSRVRLNG				102
	DGSRAVRLNGVENANTRKSSR				103
	ENANTRKSSRSNPRGRRHP				119
	TRKSSRSNPRG				
Pax2	1	10	20	30	Clone #
	STPPSREAYSRPYSVDSDSDTNAKHSSHNRRLRTRSRPN				104
	STPPSREAYSRPYSVDSDSD				105
	SRPYSVDSDSDTNAKHSSHNR				106
	TNAKHSSHNRRLRTRSRPN				
DCX8	1	10	20	30	Clone #
	RYKHDIGCDAGVDKKSSSVRGCGAHSSPPRAGRGRGTMTVSRL				107
	RYKHDIGCDAGVDKKSSSVRGCG				108
	GCDAGVDKKSSSVRGCGAHSSPPRA				109
	GAHSSPPRAGRGRGTMTVSRL				

FIG.5B

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EXPRESSION OF PHAGE INSERTS AS GST FUSION

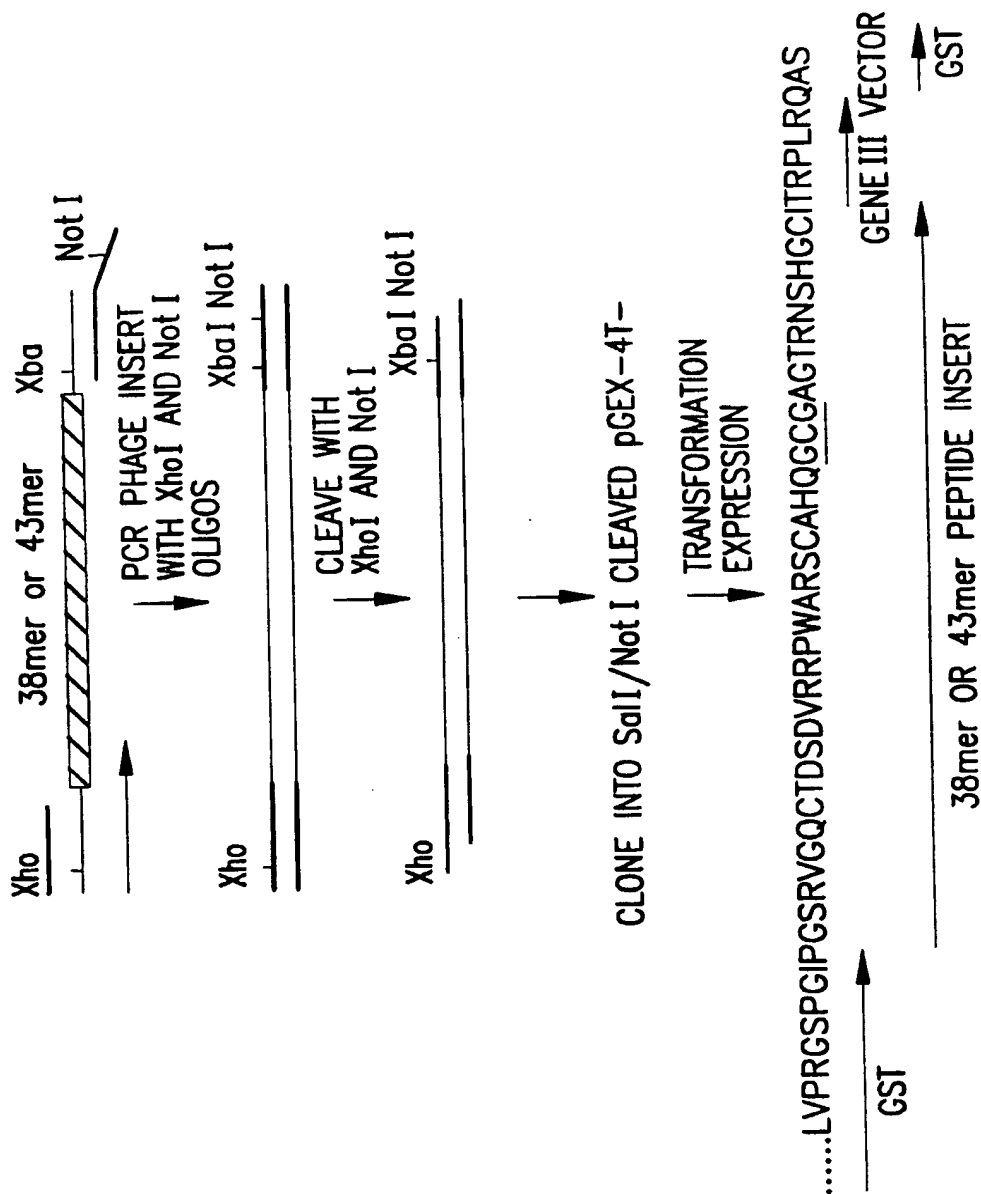


FIG. 5A

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1021 gagatgagat ccaagtaa at aagacccaaa tcccggacac ggtcacacaa tactcggagc
R D E I Q V N K T Q I P D T V T Q Y S E
1081 tgtaccatga cttcaccacc acgcaggtgg gaatgcacga cattgtccgc agcttccggc
L Y H D F T T T Q V G M H D I V R S F R
1141 agaccatgga ccaatacagc acggagcccg gcagatacag gttcatgggg actgaagcct
Q T M D Q Y S T E P G R Y R F M G T E A
1201 atgcagagag tattgacagg accgtgatgt actatggatt gccatttatc caagaagctg
Y A E S I D R T V M Y Y G L P F I Q E A
1261 attttccatt caacaattac ctcagcatgc tagacactgt ttctgggaac agcgtgtatg
D F P F N N Y L S M L D T V S G N S V Y
1321 aggttatcac atcctggatg gaaaacatgc cagaaggaaa atggcctaac tggatgattg
E V I T S W M E N M P E G K W P N W M I
1381 gtggaccaga cagttcacgg ctgacttcgc gtttggggaa tcagtatgtc aacgtgatga
G G P D S S R L T S R L G N Q Y V N V M
1441 acatgcttct tttcacactc cctggaactc ctataactta ctatggagaa gaaattggaa
N M L L F T L P G T P I T Y Y G E E I G
1501 tgggaaatat tgtagccgca aatctcaatg aaagctatga tattastacc cttcgtcaa
M G N I V A A N L N E S Y D I N T L R S
1561 agtcaccaat gcagtgggac aatagttcaa atgctggttt ttctgaagct agtaacacct
K S P M Q W D N S S N A G F S E A S N T
1621 ggttacctac caattcagat taccacactg tgaatgttga tgtccaaaag actcagccca
W L P T N S D Y H T V N V D V Q K T Q P
1681 gatcggcttt gaagttatat caagatttaa gtctacttca tgccaatgag ctactcctca
R S A L K L Y Q D L S L L H A N E L L L
1741 acaggggctg gttttgcat ttgaggaatg acagccacta tgttgtgtac acaagagagc
N R G W F C H L R N D S H Y V V Y T R E
1801 tggatggcat cgacagaatc tttatcgtgg ttctgaattt tggagaatca acactgttaa
L D G I D R I F I V V L N F G E S T L L
1861 atctacataa tatgatttcg ggccttcccg ctaaaataag aataaggtta agtaccaatt
N L H N M I S G L P A K I R I R L S T N
1921 ctgccgacaa aggcagtaaa gttgatacaa gtggcatttt tctggacaag ggagagggac
S A D K G S K V D T S G I F L D K G E G
1981 tcattcttga acacaacacg aagaatctcc ttcacgcca aacagctttc agagatagat
L I F E H N T K N L L H R Q T A F R D R
2041 gctttgtttc caatcgagca tgctattcca gtgtactgaa catactgtat acctcgtgtt
C F V S N R A C Y S S V L N I L Y T S C
2101 aggcaccttt atgaagagat gaagacactg gcatttcagt gggattgtaa gcatttgtaa
2161 tagcttcatg tacagcatgc tgcttggtga acaatcatta attcttcgat atttctgtag
2221 cttgaatgta accgctttta gaaaggttct caaatgtttt gaaaaaata aaatgtttta
2281 aagt

FIG.4B

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1 gccttactgc aggaaggcac tccgaagaca taagtcggtg agacatggct gaagataaaa
M A E D K
61 gcaagagaga ctccatcgag atgagtatga agggatgcca gacaaacaac gggtttgtcc
S K R D S I E M S M K G C Q T N N G F V
121 ataatgaaga cattctggag cagaccccgg atccaggcag ctcaacagac aacctgaagc
H N E D I L E Q T P D P G S S T D N L K
181 acagcaccag gggcatcctt ggctcccagg agcccgactt caagggcgtc cagccctatg
H S T R G I L G S Q E P D F K G V Q P Y
241 cggggatgcc caaggagggtg ctgttccagt tctctggcca ggcccgtac cgcatacctc
A G M P K E V L F Q F S G Q A R Y R I P
301 gggagatcct cttctggctc acagtggctt ctgtgctggt gctcatcgcg gccaccatag
R E I L F W L T V A S V L V L I A A T I
361 ccatcattgc cctctctcca aagtgcctag actggtggca ggaggggccc atgtaccaga
A I I A L S P K C L D W W Q E G P M Y Q
421 tctaccaag gtctttcaag gacagtaaca aggatgggaa cgagatctg aaaggatttc
I Y P R S F K D S N K D G N G D L K G I
481 aagataaact ggactacatc acagctttaa atataaaaac tgtttggatt acttcatttt
Q D K L D Y I T A L N I K T V W I T S F
541 ataaatcgct ccttaaagat ttcagatag gtgttgaaga tttccgggaa gttgatccca
Y K S S L K D F R Y G V E D F R E V D P
601 tttttggaac gatggaagat tttgagaatc tggttgcagc catacatgat aaaggtttaa
I F G T M E D F E N L V A A I H D K G L
661 aattaatcat cgatttcata ccaaaccaca cgagtgataa acatatttgg tttcaattga
K L I I D F I P N H T S D K H I W F Q L
721 gtcggacacg gacaggaaaa tatactgatt attatatctg gcatgactgt acccatgaaa
S R T R T G K Y T D Y Y I W H D C T H E
781 atggcaaaac cattccaccc aacaactggt taagtgtgta tggaaactcc agttggcact
N G K T I P P N N W L S V Y G N S S W H
841 ttgacgaagt gcgaaaccaa tgttattttc atcagtttat gaaagagcaa cctgatttaa
F D E V R N Q C Y F H Q F M K E Q P D L
901 atttccgcaa tcctgatggt caagaagaaa taaaagaaat tttacggttc tggctcaciaa
N F R N P D V Q E E I K E I L R F W L T
961 aggggtgttga tggttttagt ttggatgctg ttaaattcct cctagaagca aagcacctga
K G V D G F S L D A V K F L L E A K H L

FIG.4A

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1280	1300	1320
DYMERQLDFTIGEAQDLPO	FVDKIRGEGMRYIIILDPAI	SGNETKTYPAFERGOQNDVF
1340	1360	1380
VKWPNTNDICWAKVWDLPN	ITIDKTLTEDEAVNASRAHV	AFPDFFRTSTAEEWAREIVD
1400	1420	1440
FYNEKMKFDGLWIDMNEPSS	FVNGTTTNQCRNDELNYPPY	FPELTKRTDGLHFRTICMEA
1460	1480	1500
EQILSDGTSVLHYDVHNLVG	WSQMKPTHDALQKTTGKRG I	VISRSTYPTSGRWGGHWLGD
1520	1540	1560
NYARWDNMDKSIIGMMEFSL	FGISYTGADICGFFNNSEYH	LCTRWMQLGAFYPYSRNHNI
1580	1600	1620
ANTRRQDPASWNETFAEMSR	NILNIRYTLTPYFYTMHEI	HANGGTVIRPLLHEFFDEKP
1640	1660	1680
TWDIFKQFLWGPAFMVTPVL	EPYVQTVNAYVPNARWFDYH	TGKDIGVRGQFQTFNASYDT
1700	1720	1740
INLHVRGGHILPCQEPANQNT	FYSRQKHMKLIVAADDNQMA	QGSLEWDDGESIDTYERDLY
1760	1780	1800
LSVQFNLNQTTLTSTILKRG	YINKSETRLGSLHVWGKGT	PVNAVTLTYNGNKNSLPFNE
1820	1827	
DTTNMILRIDLTTHNVTL EE	PIEINWS	

FIG. 3B

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20	40	60
MARKKFSGLEISLIVLFVIV	TIIAIALIVVLATKTPAVDE	ISDSTSTPATTRVTTNPSDS
80	100	120
GKCPNVLNDPVNVRINCIPE	QFPTEGICAQRGCCWRPWND	SLIPWCFFVDNHGYNVQDMT
140	160	180
TTSIGVEAKLNRIPSPTLFG	NDINSVLFTTQNTPNRFRF	KITDPNNRRYEVPHQYVKEF
200	220	240
TGPTVSDTLVDKVAQNPF	IQVIRKSNGKTLFDTSIGPL	VYSDQYLQISARLPDYYG
260	280	300
IGEQLVHKRFRHDLWKTWPI	FTRDQLPGDNNNNLYGHQTF	FMCIEDTSGKSFGVFLMNSN
320	340	360
AMEIFIQPTPIVYRVTGGI	LDFYILLGDTPEQVVQYQQ	LVGLPAMPAYWNLGFQLSRW
380	400	420
NYKSLDVVKEVRRNREAGI	PFDTQVTDIDYMEDKKDFTY	DQVAFNGLPQFVQDLHDHGG
440	460	480
KYVIILDPASIGRRANGTT	YATYERGNTQHWINESDGS	TPIIGEVWPGLTVYPDFTNP
500	520	540
NCIDWWANECSIFHQEVQYD	GLWIDMNEVSSFIQGSTKGC	NVNKLNYPPTPDILDKLMY
560	580	600
SKTICMDAVQNWGKQYDVHS	LYGYSMAIATEQAVQKVFPN	KRSFILTRSTFAGSGRHAH
620	640	660
WLGDNSTASWEQMEWSITGML	EFSLFGIPLVGADICGFVAE	TTEELCRRWMLGAFYPSR
680	700	720
NHNSDGYEHQDPAFFGQNSL	LVKSSRQYLTIQYTLPLFLY	TLFYKAHVGETVARPVLHE
740	760	780
FYEDTNSWIEDTEFLWGPAL	LITPVLKQGADTVSAYIPDA	IWYDYESGAKRPWRKQVDM
800	820	840
YLPADKIGLHLRGYIPIQ	EPDVTSTASRKNPLGLIVAL	GENNTAKGDFWDDGETKDT
860	880	900
IQNGNYILYTFVSNNTLDI	VCTHSSYQEGTTLAFQTVKI	LGLTDSVTEVRVAENNQPMN
920	940	960
AHSNFTYDASNQVLLIADLK	LNLGRNFSVQWNQIFSENER	FNCYPDADLATEQKCTQRC
980	1000	1020
VWRTGSSLSKAPECYFPRQD	NSYSVNSARYSSMGITADLQ	LNTANARIKLPSDPISTLRV
1040	1060	1080
EVKYHKNDMLQFKIYDPQKK	RYEVPVPLNIPTTPISTYED	RLYDVEIKENPFGIQIRRRS
1100	1120	1140
SGRVIWDSWLPFAFNDQFI	QISTRLPSEYIYGFEVEHT	AFKRDLNWNTWGMFTRDQPP
1160	1180	1200
GYKLNSYGFHPYMALEEEG	NAHGVFLLNSNAMDVTFQPT	PALTYRTVGGILDFYMFLGP
1220	1240	1260
TPQVATKQYHEVIGHPVMPA	YWALGFQLCRYGYANTSEVR	ELYDAMVAANIPYDVQYTDI

FIG.3A

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2461 ctgctgacca cccttctggt gattggtata attttagcag ttgtgtttat ccgcataaag
L L T T L L V I G I I L A V V F I R I K
2521 aaggataaag gcaaagataa tggtgaaagt gctcaagcat ctgaagtcaa acctctgaga
K D K G K D N V E S A Q A S E V K P L R
2581 agctgaatth gaaaaggaat gtttgeatth atatagcaag tgctatttca gcaacaacca
S

2641 tctcatccta ttacttttca tctaacgtgc attataatth tttaaacaga tattccctct
2701 tgccttttaa tatttgctaa atatttctth tttagaggagg agtcttgctc tgcgcccag
2761 gctggagtag agtggtgtga tcccagctca ctgcaacctc cgcctcctgg gttcacatga
2821 ttctcctgcc tcagcttcct aagtagctgg gtttacaggc acccaccacc atgcccagct
2881 aatttttgta tttttaatag agacgggggt tcgccatttg gccaggatgg tcttgeactc
2941 ctgacgtcaa gtgatctgcc tgccttggtc tcccaatata ggcatagaacc actgcaccca
3001 cctacttaga tatttcatgt gctatagaca ttagagagat ttttcattth tccatgacat
3061 ttttctctc tgcaaatggc ttagctactt gtgtttttcc cttttggggc aagacagact
3121 cattaaatat tctgtacatt ttttcttht caaggagata tatcagtgtt gtctcataga
3181 actgcctgga ttccatttht gtttttctg attccatcct gtgtcccctt catccttgac
3241 tcctttggta tttcactgaa tttcaaacat ttgtcagaga agaaaaaagt gaggactcag
3301 gaaaaataaa taaataaaag aacagcctth tgcggccgcg aattc

FIG.2C

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1261 ggactcttcc taatccaaac ctatgctgga atgttacagt tagctaaaca gtccttgaag
G L F L I Q T Y A G M L Q L A K Q S L K
1321 aagcaagata ctcttcagta caacttaacg atagagggtgt ctgacaaaga tttcaagacc
K Q D T P Q Y N L T I E V S D K D F K T
1381 ctttgttttg tgcaaatcaa cggtattgat atcaatgatc agatcccat ctttgaaaaa
L C F V Q I N V I D I N D Q I P I F E K
1441 tcagattatg gaaacctgac tcttgctgaa gacacaaaca ttgggtccac catcttaacc
S D Y G N L T L A E D T N I G S T I L T
1501 atccaggcca ctgatgctga tgagccattt actgggagtt ctaaaattct gtatcatatc
I Q A T D A D E P F T G S S K I L Y H I
1561 ataaaggagg acagtgaggg acgcctgggg gttgacacag atccccatac caacaccgga
I K G D S E G R L G V D T D P H T N T G
1621 tatgtcataa ttaaaaagcc tcttgatttt gaaacagcag ctgtttccaa cattgtgttc
Y V I I K K P L D F E T A A V S N I V F
1681 aaagcagaaa atcctgagcc tctagtgttt ggtgtgaagt acaatgcaag ttcttttgcc
K A E N P E P L V F G V K Y N A S S F A
1741 aagttcacgc ttattgtgac agatgtgaat gaagcacctc aattttccca acacgtattc
K F T L I V T D V N E A P Q F S Q H V F
1801 caagcgaaag tcagtgagga tgtagctata ggcactaaag tgggcaatgt gactgccaag
Q A K V S E D V A I G T K V G N V T A K
1861 gatccagaag gtctggacat aagctattca ctgaggggag acacaagagg ttggcttaaa
D P E G L D I S Y S L R G D T R G W L K
1921 attgaccacg tgactggtga gatctttagt gtggctccat tggacagaga agccggaagt
I D H V T G E I F S V A P L D R E A G S
1981 ccatatcggg tacaagtggg ggccacagaa gtaggggggt cttccttaag ctctgtgtca
P Y R V Q V V A T E V G G S S L S S V S
2041 gagttccacc tgatccttat ggatgtgaat gacaaccctc ccaggctagc caaggactac
E F H L I L M D V N D N P P R L A K D Y
2101 acgggcttgt tcttctgcca tcccctcagt gcacctggaa gtctcatttt cgaggctact
T G L F F C H P L S A P G S L I F E A T
2161 gatgatgatc agcacttatt tcgggggtccc cattttacat tttccctcgg cagtggaagc
D D D Q H L F R G P H F T F S L G S G S
2221 ttacaaaacg actgggaagt ttccaaaatc aatgggtactc atgcccgact gtctaccagg
L Q N D W E V S K I N G T H A R L S T R
2281 cacacagact ttgaggagag ggcgtatgtc gtcttgatcc gcatcaatga tgggggtcgg
H T D F E E R A Y V V L I R I N D G G R
2341 ccacccttgg aaggcattgt ttctttacca gttacattct gcagttgtgt ggaaggaagt
P P L E G I V S L P V T F C S C V E G S
2401 tgtttccggc cagcaggtca ccagactggg ataccactg tgggcatggc agttggtata
C F R P A G H Q T G I P T V G M A V G I

FIG.2B

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1  gaattccgtc tgcaccactg aatggaagaa aaggactttt aaccaccatt ttgtgactta
61  cagaaaggaa tttgaataaa gaaaactatg atacttcagg cccatcttca ctccctgtgt
      M I L Q A H L H S L C
121 cttcttatgc tttatttggc aactggatat ggccaagagg ggaagttag tggacccttg
      L L M L Y L A T G Y G Q E G K F S G P L
181 aaacccatga ctttttctat ttatgaaggc caagaaccga gtcaaattat attccagttt
      K P M T F S I Y E G Q E P S Q I I F Q F
241 aaggccaatc ctctgctgt gacttttgaa ctaactgggg agacagacaa catatttggt
      K A N P P A V T F E L T G E T D N I F V
301 atagaacggg agggacttct gtattacaac agagccttgg acagggaac aagatctact
      I E R E G L L Y Y N R A L D R E T R S T
361 cacaatctcc aggttgcagc cctggacgct aatggaatta tagtggaggg tccagtcctt
      H N L Q V A A L D A N G I I V E G P V P
421 atcaccatag aagtgaagga catcaacgac aatcgaccca cgtttctcca gtcaaagtac
      I T I E V K D I N D N R P T F L Q S K Y
481 gaaggctcag taaggcagaa ctctcgccca ggaaagccct tcttgatgt caatgccaca
      E G S V R Q N S R P G K P F L Y V N A T
541 gacctggatg atccggccac tccaatggc cagctttatt accagattgt catccagctt
      D L D D P A T P N G Q L Y Y Q I V I Q L
601 cccatgatca acaatgtcat gtactttcag atcaacaaca aaacgggagc catctctctt
      P M I N N V M Y F Q I N N K T G A I S L
661 acccgagagg gatctcagga attgaatcct gctaagaatc cttcctataa tctggtgatc
      T R E G S Q E L N P A K N P S Y N L V I
721 tcagtgaagg acatgggagg ccagagttag aattccttca gtgataccac atctgtggat
      S V K D M G G Q S E N S F S D T T S V D
781 atcatagtga cagagaatat ttggaaagca ccaaaacctg tggagatggt ggaaaactca
      I I V T E N I W K A P K P V E M V E N S
841 actgatcctc acccatcaa aatcactcag gtgcggtgga atgatcccg tgcacaatat
      T D P H P I K I T Q V R W N D P G A Q Y
901 tccttagttg acaaagagaa gctgccaaga ttcccathtt caattgacca ggaaggagat
      S L V D K E K L P R F P F S I D Q E G D
961 atttacgtga ctgagccctt ggaccgagaa gaaaaggatg catatgtttt ttatgcagtt
      I Y V T Q P L D R E E K D A Y V F Y A V
1021 gcaaaggatg agtacggaaa accactttca tatccgctgg aaattcatgt aaaagttaaa
      A K D E Y G K P L S Y P L E I H V K V K
1081 gatattaatg ataatccacc tacatgtccg tcaccagtaa ccgtatttga ggtccaggag
      D I N D N P P T C P S P V T V F E V Q E
1141 aatgaacgac tgggtaacag tatcgggacc cttactgcac atgacaggga tgaagaaaat
      N E R L G N S I G T L T A H D R D E E N
1201 actgccaaca gttttctaaa ctacaggatt gtggagcaaa ctcccaaact tcccatggat
      T A N S F L N Y R I V E Q T P K L P M D

```

FIG.2A

1/48

20 40 60
MGMSKSHSFFGYPLSIFIV VNEFCERFSYYGMRAILILY FTNFISWDDNLSTAIYHTFV

80 100 120
ALCYLTPILGALIADSWLGK FKTIVSLSIVYTIGQAVTSV SSINDLTDHNDGTPDSLPLV

140 160 180
HVVLSLIGLALIALGTGGIK PCVSAFGGDQFEEGQEKQRN RFFSIFYLAINAGSLLSTII

200 220 240
TPMLRVQCGIHSKQACYPL AFGVPAALMAVALIVFVLGS GMYKKFKPQGNIMGKVAKCI

260 280 300
GFAIKNRFRHRSAFPKREH WLDWAKEKYDERLISQIKMV TRVMFLYIPLPMFWALFDQQ

320 340 360
GSRWTLQATTMSGKIGALEI QPDQMOTVNAILIVIMVPIF DAVLYPLIAKCGFNFTSLKK

380 400 420
MAVGMVLASMAFVVAIVQV EIDKTLPVFPKGNEVQIKVL NIGNNTMNISLPGEMVTLGP

440 460 480
MSQTNAFMTFDVNKLTRINI SSPGSPVTAVTDDFKQGQRH TLLVWAPNHYQVVKDGLNQK

500 520 540
PEKGENGIRFVNTFNELITI TMSGKVYANISSYNASTYQF FPSGIKGFTISSTEIPPOCQ

560 580 600
PNFNTFYLEFGSAYTYIVQR KNDSCPEVKVFEDISANTVN MALQIPQYFLLTCGEVVFSV

620 640 660
TGLEFSYSQAPSNMKSVLQA GWLLTVAVGNIIIVLIVAGAG QFSKQWAEYILFAALLLVVC

680 700 708
VIFAIMARFYTYINPAEIEA QFDEDEKKNRLEKSNPYFMS GANSQKQM

FIG. 1

91. The composition of claim 28 for use as a medicament.

92. The composition of claim 29 for use as a medicament.

93. The composition of claim 81 for use as a medicament.

10 94. The composition of claim 23 in which the drug is insulin or leuprolide.

95. The composition of claim 24 in which the active agent is insulin or leuprolide.

15

96. The composition of claim 25 in which the drug is insulin or leuprolide.

97. The composition of claim 28 in which the drug
20 is insulin or leuprolide.

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30

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification⁶ : A61K 38/00, 38/02, C07K 5/00, 7/00</p>	<p>A3</p>	<p>(11) International Publication Number: WO 98/51325 (43) International Publication Date: 19 November 1998 (19.11.98)</p>																																																																								
<p>(21) International Application Number: PCT/US98/10088 (22) International Filing Date: 15 May 1998 (15.05.98) (30) Priority Data: 60/046,595 15 May 1997 (15.05.97) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/046,595 (CIP) Filed on 15 May 1997 (15.05.97) (71) Applicants (for all designated States except US): CYTOGEN CORPORATION [US/US]; 600 College Road East, Princeton, NJ 08540 (US). ELAN CORPORATION, PLC [IE/IE]; Lincoln House, Lincoln Place, Dublin 2 (IE). (72) Inventors; and (75) Inventors/Applicants (for US only): ALVAREZ, Vernon, L. [US/US]; 187 Rice Drive, Morrisville, PA 19067 (US). O'MAHONY, Daniel, J. [IE/IE]; 75 Avoca Park, Avoca Avenue, Blackrock, Dublin (IE). LAMBKIN, Imelda, J. [IE/IE]; 9 Station Road, Sutton, Dublin 13 (IE). PATTERSON, Catherine, A. [GB/IE]; 3 Grange Crescent, Pottery Road, Dunlaoghaire, Dublin (IE). SINGLETON, Ju-</p>		<p>dith [US/US]; Knoll Way, Rocky Way, NJ 08553 (US). BELINKA, Benjamin, A., Jr. [US/US]; 15 Pelham Road, Kendall Park, NJ 08824 (US). CARTER, John, M. [US/US]; 35 Chicory Lane, Trenton, NJ 08638-1926 (US). CAGNEY, Gerard, M. [IE/US]; 2618 Yale Avenue East, Seattle, WA 98102 (US). (74) Agents: ANTLER, Adriane, M. et al.; Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036 (US). (81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, GW, HU, ID, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments. (88) Date of publication of the international search report: 17 December 1998 (17.12.98)</p>																																																																								
<p>(54) Title: RANDOM PEPTIDES THAT BIND TO GASTRO-INTESTINAL TRACT (GIT) TRANSPORT RECEPTORS AND RELATED METHODS</p>																																																																										
<p>(57) Abstract</p>																																																																										
<p>This invention relates to proteins (e.g., peptides) that are capable of facilitating transport of an active agent through a human or animal gastro-intestinal tissue, and derivatives (e.g., fragments) and analogs thereof, and nucleotide sequences coding for said proteins and derivatives. The proteins of the invention have use in facilitating transport of active agents from the luminal side of the GIT into the systemic blood system, and/or in targeting active agents to the GIT. Thus, for example, by binding (covalently or noncovalently) a protein of the invention to an orally administered drug, the drug can be targeted to specific receptor sites or transport pathways which are known to operate in the human gastro-intestinal tract, thus facilitating its absorption into the systemic system.</p> <table border="0" data-bbox="805 1186 1430 1976"> <tr> <td>20</td> <td>40</td> <td>60</td> </tr> <tr> <td>MGMSKSHSFFGYPLSIFIV</td> <td>VNEFCERFSYYGMRAILILY</td> <td>FTNFISWDDNLSTAIYHTFV</td> </tr> <tr> <td>80</td> <td>100</td> <td>120</td> </tr> <tr> <td>ALCYLTPILGALIADSWLKG</td> <td>FKTIVLSIIVYTIGQAVTSV</td> <td>SSINDLTDHNDGTPDLSLV</td> </tr> <tr> <td>140</td> <td>160</td> <td>180</td> </tr> <tr> <td>HVVLISLIGLALIALGTGGIK</td> <td>PCVSAFGGDQFEEGQEKQRN</td> <td>RFFSIFYLAINAGSLLSTII</td> </tr> <tr> <td>200</td> <td>220</td> <td>240</td> </tr> <tr> <td>TPMLRVQCGIHSKOACYPL</td> <td>AFGVPAALMAVALIVFVLGS</td> <td>GMYYKFKPQGNIMGKVAKCI</td> </tr> <tr> <td>260</td> <td>280</td> <td>300</td> </tr> <tr> <td>GFAIKNRFRHRSKAFPKREH</td> <td>WLDWAKEKYDERLISQIKMV</td> <td>TRVMFLYIPLPMFWALFDQ</td> </tr> <tr> <td>320</td> <td>340</td> <td>360</td> </tr> <tr> <td>GSRWLTQATTMSGKIGALEI</td> <td>QPDQMQTVNAILIIVMPLIF</td> <td>DAVLYPLIAKCGFNFTSLKK</td> </tr> <tr> <td>380</td> <td>400</td> <td>420</td> </tr> <tr> <td>MAVGMVLASMAFVVAATVQV</td> <td>EIDKTLVPVFKGNEVQIKVL</td> <td>NIGNNTMNISLPGEMVTLGP</td> </tr> <tr> <td>440</td> <td>460</td> <td>480</td> </tr> <tr> <td>MSQTNAFMFTDVNKLTRINI</td> <td>SSPGSPVTAVTDDFKQGQRH</td> <td>TLLVWAPNHQVVKDGLNQK</td> </tr> <tr> <td>500</td> <td>520</td> <td>540</td> </tr> <tr> <td>PEKGENGIRFVNTFNEIITI</td> <td>TMSGKVYANISSYASTYQF</td> <td>FPSGIGFTISSTEIPPQCO</td> </tr> <tr> <td>560</td> <td>580</td> <td>600</td> </tr> <tr> <td>PNFNTFYLEFGSAYTYIVQR</td> <td>KNDSCPEVKVFEDISANTVN</td> <td>MALQIPQYFLLTQGEVVFVSV</td> </tr> <tr> <td>620</td> <td>640</td> <td>660</td> </tr> <tr> <td>TGLEFSYSQAPSNNKSVLQA</td> <td>GWLLTVAVGNIIVLIVAGAG</td> <td>QFSKQWAEYILFAALLLVVC</td> </tr> <tr> <td>680</td> <td>700</td> <td>708</td> </tr> <tr> <td>VIFAIMARFYTYINPAEIEA</td> <td>QFDEDEKKNRLEKSNPYFMS</td> <td>GANSQKQM</td> </tr> </table>			20	40	60	MGMSKSHSFFGYPLSIFIV	VNEFCERFSYYGMRAILILY	FTNFISWDDNLSTAIYHTFV	80	100	120	ALCYLTPILGALIADSWLKG	FKTIVLSIIVYTIGQAVTSV	SSINDLTDHNDGTPDLSLV	140	160	180	HVVLISLIGLALIALGTGGIK	PCVSAFGGDQFEEGQEKQRN	RFFSIFYLAINAGSLLSTII	200	220	240	TPMLRVQCGIHSKOACYPL	AFGVPAALMAVALIVFVLGS	GMYYKFKPQGNIMGKVAKCI	260	280	300	GFAIKNRFRHRSKAFPKREH	WLDWAKEKYDERLISQIKMV	TRVMFLYIPLPMFWALFDQ	320	340	360	GSRWLTQATTMSGKIGALEI	QPDQMQTVNAILIIVMPLIF	DAVLYPLIAKCGFNFTSLKK	380	400	420	MAVGMVLASMAFVVAATVQV	EIDKTLVPVFKGNEVQIKVL	NIGNNTMNISLPGEMVTLGP	440	460	480	MSQTNAFMFTDVNKLTRINI	SSPGSPVTAVTDDFKQGQRH	TLLVWAPNHQVVKDGLNQK	500	520	540	PEKGENGIRFVNTFNEIITI	TMSGKVYANISSYASTYQF	FPSGIGFTISSTEIPPQCO	560	580	600	PNFNTFYLEFGSAYTYIVQR	KNDSCPEVKVFEDISANTVN	MALQIPQYFLLTQGEVVFVSV	620	640	660	TGLEFSYSQAPSNNKSVLQA	GWLLTVAVGNIIVLIVAGAG	QFSKQWAEYILFAALLLVVC	680	700	708	VIFAIMARFYTYINPAEIEA	QFDEDEKKNRLEKSNPYFMS	GANSQKQM
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/10088

A. CLASSIFICATION OF SUBJECT MATTER IPC(6) :A61K 38/00, 38/02; C07K 5/00, 7/00 US CL :Please See Extra Sheet. According to International Patent Classification (IPC) or to both national classification and IPC																				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/2, 12, 13, 14, 15, 16, 17, 18, 21; 530/300, 324, 325, 326, 327, 328, 329, 330, 350 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) APS, CAS ONLINE, BIOSIS, MEDLINE, EMBASE, WPIDS																				
C. DOCUMENTS CONSIDERED TO BE RELEVANT																				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.																		
Y	SAITO et al. Cloning and Characterization of a pH-Sensing Regulatory Factor That Modulates Transport Activity of the Human H ⁺ /Peptide Cotransporter, PEPT1. Biochem. and Biophys. Res. Commun. 1997, Vol. 237, pages 577-582, see entire document.	1																		
Y	LIANG et al. Human Intestinal H ⁺ /Peptide Cotransporter: Cloning, Functional Expression, and Chromosomal Localization. The Journal of Biological Chemistry. 24 March 1995, Vol. 270, No. 12, pages 6456-6463, see entire document.	1																		
Y	US 5,338,665 A (SCHATZ et al.) 16 August 1994, see especially Figure 3A.	18-20																		
Y	WO 95/29938 A1 (FERRING AB) 09 November 1995, see especially page 34 (Seq ID No.s 4 and 5) and page 37 (Seq ID No. 21).	18-20																		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.																				
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